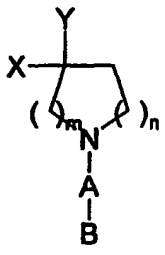




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C07D 211/00</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 00/27815</b> <b>(43) International Publication Date:</b> 18 May 2000 (18.05.00)
<b>(21) International Application Number:</b> PCT/EP99/08706 <b>(22) International Filing Date:</b> 10 November 1999 (10.11.99)  <b>(30) Priority Data:</b> MI98A002442 11 November 1998 (11.11.98) IT  <b>(71) Applicant (for all designated States except US):</b> SMITHKLINE BEECHAM SPA [IT/IT]; Via Zambelletti, I-20021 Baranzate di Bollate (IT).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BARLOCCO, Daniela [IT/IT]; Università degli Studi di Milano, Istituto di Chimica Farmaceutica E Tossicologica, Viale Abruzzi, 42, I-20131 Milan (IT). CIGNARELLA, Giorgio [IT/IT]; Università degli Studi di Milano, Istituto di Chimica Farmaceutica E Tossicologica, Viale Abruzzi, 42, I-20131 Milan (IT). GIARDINA, Guiseppe, Arnaldo, Maria [IT/IT]; SmithKline Beecham Spa, Via Zambelletti, I-20021 Baranzate di Bollate (IT). GRUGNI, Mario [IT/IT]; SmithKline Beecham Spa, Via Zambelletti, I-20021 Baranzate di Bollate (IT). RONZONI, Silvano [IT/IT]; SmithKline Beecham Spa, Via Zambelletti, I-20021 Baranzate di Bollate (IT).		<b>(74) Agent:</b> RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).  <b>(81) Designated States:</b> CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> NOVEL COMPOUNDS  <b>(57) Abstract</b> <p>Compounds of formula (I) or a salt thereof or a hydrate thereof, wherein X and Y are selected independently from hydrogen and aryl, which aryl is unsubstituted or substituted one or more times by hydroxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, aryl, heterocyclyl, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or halo, which alkyl or alkoxy groups are unsubstituted or substituted one or more times by halo; m and n are independently 0 to 3, provided that m and n are not both 0; A represents a single bond or is -(CR<sub>pa</sub>R<sub>pb</sub>)<sub>p</sub> wherein p is 1-3 and R<sub>pa</sub> and R<sub>pb</sub> are selected independently from hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy and halo, which alkyl or alkoxy groups are independently substituted one or more times by halo; B represents a C<sub>4-8</sub> saturated or unsaturated ring, which ring is unsubstituted or substituted one or more times by C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, aryl, aryloxy, hydroxy, oxo, halo, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, and C<sub>1-6</sub>alkylamido, which C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy groups are unsubstituted or substituted one or more times by halo, which aryl group is unsubstituted or substituted one or more times by aryl, heterocyclyl, aryloxy, arylC<sub>1-6</sub>alkoxy, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkenoxy, C<sub>1-6</sub>alkoxy, halo, or C<sub>1-6</sub>, which C<sub>1-6</sub>alkyl may be substituted one or more times by halo, and which aryl group is linked to said ring by a single bond or is benzo-condensed therewith are ligands of the ORL-1 receptor.</p> <div style="text-align: center;">  <p>(I)</p> </div>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

## NOVEL COMPOUNDS

The present invention relates to certain novel compounds, to processes for preparing such compounds, to pharmaceutical compositions containing such compounds, and to the use of such compounds in medicine.

The ORL-1 receptor is found throughout the whole of the neuraxis and is known to be involved in the transmission of pain.

European Patent Application EP-A-0856514 (F. Hoffmann-LaRoche AG) discloses 8-substituted-1,3,8-triaza-spiro[4.5]decan-4-one derivatives that are agonists and/or antagonists of the ORL-1 receptor. Said ORL-1 receptor is also known as the nociceptin/OFQ receptor.

Eur. J. Med. Chem. 1978;13:533-547 (Eirin *et al.*) discloses ( $\pm$ )-3-[(4-phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene for use as a neuroleptic agent.

An. Real. Acad. Farm. 1989;55:461-469 (Santana *et al.*) discloses ( $\pm$ )-2-[(4-phenylpiperidin-1-yl)methyl]-1,2,3,4-tetrahydronaphthalene as an antidopaminergic agent.

United States Patent US-A-3812119 (Ciba-Geigy Corporation) discloses certain dibenzocycloheptenes that have utility as antidepressants.

United States Patent US 4022791 (Pfizer Inc.) discloses certain 2-aminomethyl-3,4-dihydronaphthalenes as analgesics.

J. Med. Chem. 1977;20(5):699-705 (Welch *et al.*) discloses 5,8-disubstituted 1-tetralones as analgesics and tranquillisers.

J. Med. Chem. 1978;21(3):257-263 (Welch *et al.*) discloses certain 5,8-disubstituted 2-aminomethyl-3,4-dihydronaphthalenes as analgesics and tranquillisers.

International Application Publication Number WO 98/36749 (Bristol-Myers Squibb) discloses certain tetralone derivatives as antiarrhythmic agents.

United Kingdom Patent Application GB2177084 (Imperial Chemical Industries PLC) discloses certain benzopyran derivatives as fungicides.

United Kingdom Patent Application GB2177085 (Imperial Chemical Industries PLC) discloses certain benzocycloalkylmethylamines as fungicides.

Co-pending International Application Publication Number WO 99/06397 (Abbott Laboratories) discloses certain piperidine compounds useful as endothelin antagonists.

International Application Publication Number WO 98/02432 (Takeda Chemical Industries Ltd) discloses certain phenylpiperidino compounds useful for the treatment of lower urinary tract infections.

International Application Publication Number WO 96/22977 discloses

certain piperidinyl derivatives for treating symptoms of ischaemic diseases and preventing cytotoxic calcium overload.

International Application Publication Number WO 97/23458 (Cocensys Inc.) discloses certain tetrahydronaphthyl and piperidine derivatives as sub-type selective N-methyl-D-aspartame receptor ligands.

Unites States Patent US 5436255 (Pfizer Inc.) discloses certain 3-piperidino-1-chromanol derivatives for blocking the NMDA receptor site.

International Application Publication Number WO 95/00131 (University of Virginia Commonwealth) discloses certain amine derivatives as useful in the treatment of CNS disorders.

European Patent Application EP 0 745 598 (Adir et Compagnie) discloses certain piperazine, piperidine, and tetrahydropyridine compounds as ligands of the D<sub>4</sub> dopamine receptor.

European Patent Application EP 0 742 207 (Eisai Co. Ltd.) discloses certain cyclic amines as having acetylcholine esterase activity.

United States patent US 5215989 (Merck & Co. Inc.) discloses certain disubstituted piperazine and imidazole derivatives useful as Class III antiarrhythmic agents.

International Application Publication Number WO 93/00313 (University of Virginia Commonwealth) discloses certain amine derivatives as selective sigma receptor binding agents.

European Patent Application EP 0 479 601 (Ajinomoto KK) discloses certain piperidine derivatives as antiarrhythmic agents.

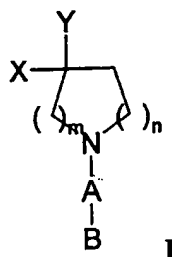
Japanese Patent Application JP 2169 569 (Eisai KK) discloses certain cyclic amine derivatives for the treatment or prophylaxis of e.g. senile dementia, cerebral apoplexy, and cerebral atherosclerosis.

It has now been found that certain nitrogen heterocycles are ligands of the ORL-1 receptor, and therefore may be useful as an analgesic in humans or animals for the treatment, for example, of acute pain; chronic neuropathic or inflammatory pain, including post herpetic neuralgia, neuralgia, diabetic neuropathy and post stroke pain; osteoarthritis/back pain; and painful pregnancy labour.

These compounds may also therefore be useful in the treatment or prophylaxis of eating disorders, such as anorexia and bulimia; anxiety and stress conditions; immune system diseases; cardiovascular system dysfunctions; memory loss, cognitive disorders, motor impairment and neurodegeneration owing to Alzheimer's disease, senile dementia, Parkinson's disease or other neurodegenerative pathologies; stroke; epilepsy; altered diuresis and sodium excretion; syndrome of inappropriate secretion of antidiuretic hormone (SIADH); adult respiratory distress syndrome (ARDS); congestive heart failure; cirrhosis

with ascites; sexual dysfunctions including impotence and frigidity; and altered pulmonary function, including chronic obstructive pulmonary disease.

Accordingly, the present invention provides a compound of formula I



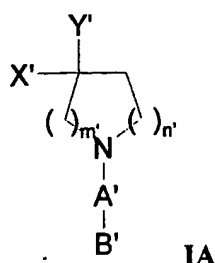
5

or a salt thereof or a hydrate thereof

wherein

- X and Y are selected independently from hydrogen and aryl, which aryl is  
 10 unsubstituted or substituted one or more times by hydroxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, aryl, heterocyclyl, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or halo, which alkyl or alkoxy groups are unsubstituted or substituted one or more times by halo;  
 m and n are independently 0 to 3, provided that m and n are not both 0;  
 15 A represents a single bond or is -(CR<sub>pa</sub>R<sub>pb</sub>)<sub>p</sub>- wherein p is 1-3 and R<sub>pa</sub> and R<sub>pb</sub> are selected independently from hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy and halo, which alkyl or alkoxy groups are independently substituted one or more times by halo;  
 B represents a C<sub>4-8</sub> saturated or unsaturated ring, which ring is unsubstituted or substituted one or more times by C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkenoxy, aryl, aryloxy,  
 20 hydroxy, oxo, halo, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, and C<sub>1-6</sub>alkylamido, which C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy groups are unsubstituted or substituted one or more times by halo, which aryl group is unsubstituted or substituted one or more times by aryl, heterocyclyl, aryloxy, arylC<sub>1-6</sub>alkoxy, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkenoxy, C<sub>1-6</sub>alkoxy, halo, or C<sub>1-6</sub>alkyl,  
 25 which C<sub>1-6</sub>alkyl may be substituted one or more times by halo, and which aryl group is linked to said ring by a single bond or is benzo-condensed therewith;  
 subject to the proviso that the compounds on the list below (hereinafter referred to as List A) are excluded:  
 10-[(4-phenylpiperidin-1-yl)methyl]-10,11-dihydro-5H-dibenzo[a,d]cycloheptene;  
 30 2-[(4-phenylpiperidin-1-yl)methyl]-6-methoxy-2-methyl-1-oxo-2H-3,4-dihydronaphthalene;  
 2-[(4-phenylpiperidin-1-yl)methyl]-6-methoxy-1-oxo-2H-3,4-dihydronaphthalene;  
 2-[(4-phenylpiperidin-1-yl)methyl]-5-methoxy-1-oxo-2H-3,4-dihydronaphthalene;

- 2-[(4-phenylpiperidin-1-yl)methyl]-6-ethyl-1-oxo-2H-3,4-dihydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-6-benzyloxy-1-oxo-2H-3,4-  
dihydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-1-oxo-6-phenylethoxy-2H-3,4-  
5 dihydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-1-oxo-6-phenoxy-2H-3,4-dihydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-1-oxo-6-phenyl-2H-3,4-dihydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-5-methoxy-2-methyl-1-oxo-2H-3,4-  
dihydronaphthalene;  
10 2-[(4-phenylpiperidin-1-yl)methyl]-2-methyl-1-oxo-6-phenoxy-2H-3,4-  
dihydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-2-methyl-1-oxo-6-phenyl-2H-3,4-  
dihydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-1-hydroxy-6-methoxy-1,2,3,4-  
15 tetrahydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-1-hydroxy-6-methoxy-2-methyl-1,2,3,4-  
tetrahydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-1-hydroxy-6-(2-phenyl)benzyloxy-1,2,3,4-  
tetrahydronaphthalene;  
20 2-[(4-phenylpiperidin-1-yl)methyl]-1-acetamido-6-methoxy-2-methyl-1,2,3,4-  
tetrahydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-1-amino-6-methoxy-2-methyl-1,2,3,4-  
tetrahydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-1,2,3,4-tetrahydronaphthalene;  
25 2-[(4-phenylpiperidin-1-yl)methyl]-7-fluoro-1,2,3,4-tetrahydronaphthalene;  
3-[(4-phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene;  
3-[(4-phenylpiperidin-1-yl)methyl]-6-fluoro-1-oxo-2H-3,4-dihydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-6-methoxy-1,2,3,4-tetrahydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene;  
30 2-[(4-phenylpiperidin-1-yl)methyl]-8-chloro-5-methoxy-2H-3,4-  
dihydronaphthalene;  
2-[(4-phenylpiperidin-1-yl)methyl]-8-chloro-5-methoxy-1-oxo-2H-3,4-  
dihydronaphthalene, and;  
2-[(4-phenylpiperidin-1-yl)methyl]-5-methoxy-1-oxo-2H-2,3-dihydroindene.  
35 There exists a further group of compounds of formula IA



wherein

X', Y', A', B', m', and n' are as defined for X, Y, A, B, m, and n respectively in formula I,

but which includes the compounds of List A.

Compounds of formula I and formula IA may exhibit stereoisomerism by virtue of the presence of chiral atoms and/or multiple bonds. The present invention therefore extends to the stereoisomers of compounds of formula I,

including racemates, enantiomers, diastereoisomers, and geometrical isomers. It has been found that, where a compound of formula I or formula IA exhibits optical isomerism, one enantiomer possesses a greater affinity for the ORL-1 receptor than its antipode.

Accordingly, the present invention also provides an enantiomer of a compound of formula I.

In a further aspect, the present invention provides a mixture of enantiomers of a compound of formula I wherein one enantiomer is present in a greater proportion than its antipode.

As has previously been mentioned, compounds of formula I are ligands of the ORL-1 receptor. Compounds of formula IA are also ligands of the ORL-1 receptor.

Thus, there is provided a compound of formula I as an active therapeutic substance.

According to another aspect of the present invention there is provided a method of modulating the ORL-1 receptor activity in a human or animal patient in need thereof, which method comprises administering to the human or animal patient an effective amount of a compound of formula IA.

In yet another aspect of the present invention there is provided the use of a compound of formula IA in the manufacture of a medicament for administration to a human or animal patient for modulating the ORL-1 receptor activity.

Said compounds of formula I and formula IA may be agonists or antagonists of the ORL-1 receptor.

In accordance with a particular aspect of the present invention, an antagonist

of formula I may be used as an analgesic in humans or animals for the treatment, for example, of acute pain; chronic neuropathic or inflammatory pain, including post herpetic neuralgia, neuralgia, diabetic neuropathy and post stroke pain; osteoarthritis/back pain; and painful pregnancy labour.

5 In accordance with a further aspect of the invention, compounds of formula I may be used in the treatment or prophylaxis of eating disorders, such as anorexia and bulimia; anxiety and stress conditions; immune system diseases; cardiovascular system dysfunctions; memory loss, cognitive disorders, motor impairment and neurodegeneration owing to Alzheimer's disease, senile dementia, Parkinson's  
10 disease or other neurodegenerative pathologies; stroke; epilepsy; altered diuresis and sodium excretion; syndrome of inappropriate secretion of antidiuretic hormone (SIADH); adult respiratory distress syndrome (ARDS); congestive heart failure; cirrhosis with ascites; sexual dysfunctions including impotence and frigidity; and altered pulmonary function, including chronic obstructive pulmonary disease.

15 In some embodiments, X and Y of formula I above may be selected independently from hydrogen and unsubstituted or substituted phenyl.

Suitably X is unsubstituted phenyl or phenyl substituted with C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, hydroxy, halo, or arylC<sub>1-6</sub>alkoxy.

Favourably, X is unsubstituted phenyl or phenyl substituted with methyl,  
20 methoxy, hydroxy, fluoro, benzyloxy, bromo, or chloro.

Preferably, X is unsubstituted phenyl, or phenyl substituted with methyl, fluoro, or chloro.

Most preferably, X is phenyl substituted with methyl.

Preferably, Y is hydrogen.

25 Suitably, m and n are independently 1 or 2, typically one of m and n is 1 and the other is 2.

Preferably m is 2 and n is 1.

Suitably, A is  $-(CR_{pa}R_{pb})_p-$  wherein p is 1-3 and R<sub>pa</sub> and R<sub>pb</sub> are selected independently from hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy and halo, which alkyl or alkoxy  
30 groups are independently substituted one or more times by halo.

Preferably A is  $-CH_2-$ .

Suitably, B represents a C<sub>4-8</sub> saturated or unsaturated ring, which ring is unsubstituted or substituted once by aryl and/or one or more times by C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkenoxo, aryloxy, hydroxy, oxo, halo, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, and C<sub>1-6</sub>alkylamido, which C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy groups are  
35 unsubstituted or substituted one or more times by halo, which aryl group is unsubstituted or substituted one or more times by aryl, heterocyclyl, aryloxy, arylC<sub>1-6</sub>alkoxy, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkenoxo, C<sub>1-6</sub>alkoxy, halo, or C<sub>1-6</sub>alkyl, which C<sub>1-6</sub>alkyl may be substituted one or



more times by halo, and wherein the aryl group is linked to said ring by a single bond or is benzo-condensed therewith.

Suitably, B represents a C<sub>4-8</sub> unsaturated ring, or a C<sub>4</sub>, C<sub>7</sub>, or C<sub>8</sub> saturated ring, which ring is unsubstituted or substituted one or more times by C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkenoxy, aryl, aryloxy, hydroxy, oxo, halo, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, and C<sub>1-6</sub>alkylamido, which C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy groups are unsubstituted or substituted one or more times by halo, which aryl group is unsubstituted or substituted one or more times by aryl, heterocyclyl, aryloxy, arylC<sub>1-6</sub>alkoxy, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkenoxy, C<sub>1-6</sub>alkoxy, halo, or C<sub>1-6</sub>alkyl, which C<sub>1-6</sub>alkyl may be substituted one or more times by halo, and wherein the aryl group is linked to said ring by a single bond or is benzo-condensed therewith.

Suitably, B represents a C<sub>4-8</sub> saturated or unsaturated ring, which ring is substituted one or more times by C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkenoxy, aryl, aryloxy, hydroxy, halo, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, and C<sub>1-6</sub>alkylamido, which C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy groups are unsubstituted or substituted one or more times by halo, which aryl group is unsubstituted or substituted one or more times by aryl, heterocyclyl, aryloxy, arylC<sub>1-6</sub>alkoxy, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkenoxy, C<sub>1-6</sub>alkoxy, halo, or C<sub>1-6</sub>alkyl, which C<sub>1-6</sub>alkyl may be substituted one or more times by halo, and wherein the aryl group is linked to said ring by a single bond or is benzo-condensed therewith.

Suitably, B represents a C<sub>4-8</sub> saturated or unsaturated ring, which ring is unsubstituted or substituted one or more times by C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkenoxy, aryl, aryloxy, hydroxy, oxo, halo, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, and C<sub>1-6</sub>alkylamido, which C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy groups are unsubstituted or substituted one or more times by halo, which aryl group is unsubstituted or substituted one or more times by aryl, heterocyclyl, aryloxy, arylC<sub>1-6</sub>alkoxy, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkenoxy, C<sub>1-6</sub>alkoxy, halo, or C<sub>1-6</sub>alkyl, which C<sub>1-6</sub>alkyl may be substituted one or more times by halo, and wherein the aryl group is linked to said ring by a single bond or is benzo-condensed therewith, provided that any benzo-condensed aryl group is substituted at least once.

Favourably, B represents a C<sub>6-7</sub> unsaturated ring or a C<sub>5-7</sub> saturated ring, which ring is unsubstituted or substituted by oxo, hydroxy, C<sub>1-6</sub>alkenoxy, or C<sub>1-6</sub>alkoxy, and is benzo-condensed with one unsubstituted or substituted aryl group, wherein suitable substituents for said aryl group are C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkyl, halo, aryl, arylC<sub>1-6</sub>alkoxy, and hydroxy.

More favourably, B is cyclohexyl, cyclohexenyl, cyclopentyl, cycloheptenyl, or cycloheptyl, either unsubstituted or substituted with hydroxy, oxo, methoxy, or 2-

propen-1-oxy, and is benzo-condensed with either phenyl or naphthyl, wherein said phenyl and naphthyl groups are either unsubstituted or substituted with methoxy, methyl, chloro, fluoro, phenyl, bromo, benzyloxy, or hydroxy.

Preferably, B is cycloheptyl either unsubstituted or substituted with hydroxy, or oxo, and is benzo-condensed with phenyl, said phenyl group being either unsubstituted or substituted with methyl, chloro, fluoro, bromo, or methoxy. More preferably, B is cycloheptyl substituted with hydroxy, and is benzo-condensed with phenyl, said phenyl group being either unsubstituted or substituted with methyl, bromo, or methoxy.

Most preferably, B is cycloheptyl substituted with hydroxy, and is benzo-condensed with phenyl, said phenyl group being substituted with methyl.

Thus, examples of B are 2,3-dihydroindene, 1,2,3,4-tetrahydronaphthalene, 1,2-dihydronaphthalene, 6,7,8,9-tetrahydro-5H-benzocycloheptene, unsubstituted or substituted by oxo, hydroxy, alkoxy, amino, dialkylamino, and/or alkylamido; or phenylcyclopentyl, phenylcyclohexyl, or phenylcycloheptyl, unsubstituted or substituted by oxo, hydroxy, alkoxy, amino, dialkylamino, or alkylamido.

"Aryl" as used herein includes C<sub>5-10</sub> aryl groups, particularly phenyl and naphthyl. C<sub>1-6</sub>alkyl groups may be linear or branched and are preferably C<sub>1-2</sub>alkyl groups, more preferably methyl. "Halo" includes chloro, bromo, and fluoro groups, especially fluoro and bromo. "Heterocyclyl" as used herein includes saturated and unsaturated heterocyclic rings.

Examples of compounds in accordance with the present invention are:

(±)-7-[(4-Phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
 (±)-7-*cis*-[(4-Phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-2-[(4-Phenylpiperidin-1-yl)methyl]-1,2-dihydronaphthalene;  
 (±)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene;  
 (R)-(-)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene;  
 (±)-2-[(4-Phenylpiperidin-1-yl)methyl]-1,2,3,4-tetrahydro naphthalene;  
 (S)-(+)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene;  
 (±)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-hydroxy-2H-3,4-dihydronaphthalene;  
 (±)-1,2-Dihydro-2-[(4-phenylpiperidin-1-yl)methyl]phenanthren-4-(3H)-one;  
 1-(2,3-Dihydro-1H-inden-2-yl)-4-phenylpiperidine;  
 (±)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-3-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-

- benzocyclohepten-5-one;  
 (±)-3-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
 (±)-*cis*-5-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene;  
 5 (±)-*trans*-5-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene;  
 2,3-Dihydro-2-[(4-phenylpiperidin-1-yl)methyl]indene;  
 N-(6,7,8,9-Tetrahydro-5H-benzocyclohepten-7-yl)-4-phenylpiperidine;  
 10 (±)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-1,3-Dimethyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-*cis*-7-[[4-(2-Methoxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 15 (±)-*cis*-3-Chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-1-Chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 20 (±)-7-[[4-(2-Hydroxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-*cis*-7-[[4-(3-Fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-*cis*-7-[[4-(2-Methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 25 (±)-*cis*-1-Methyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-*cis*-7-[[4-(4-Benzoyloxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 30 (±)-*cis*-7-[[4-(3-Bromophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-1-Fluoro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-7-[[4-(4-Fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 35 (±)-7-[[4-(3,5-Dimethoxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-*cis*-1-Phenyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;

- (±)-7-[[4-(2-Chlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*cis*-1-Bromo-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
5 (±)-1-Benzoyloxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*cis*-1-Methyl-7-[[4-(3-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*cis*-1-Methoxy-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
10 (±)-*trans*-1-Methoxy-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*cis*-1-Methoxy-7-[[4-(3-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
15 (±)-*trans*-1-Methoxy-7-[[4-(3-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*cis*-1-Hydroxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-4-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
20 (±)-1,3-Dimethyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
(±)-7-[[4-(2-Methoxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
25 (±)-3-Chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
(±)-1-Chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
(±)-7-[[4-(2-Hydroxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
30 (±)-1-Methyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
(±)-7-[[4-(2-Methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
35 (±)-7-[(4-Phenylpiperidin-1-yl)methyl]-6,7-dihydro-5H-benzocycloheptene;  
7-[(4-Phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene;  
7-[[4-(2-Methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene;  
(±)-*cis*-5-Allyloxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-

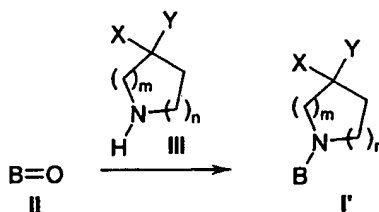
- benzocycloheptene;  
 (±)-*trans*-7-[(4-Phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-*cis*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 5 (±)-*trans*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (+)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
 10 (-)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
 (+)-*cis*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (-)-*cis*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 15 (+)-*trans*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (-)-*trans*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 20 [4-(2-Methylphenyl)-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-7-yl)]piperidine;  
 (-)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol, and;  
 (+)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol.  
 25 Especially preferred compounds are:  
 (±)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-*cis*-7-[[4-(3-Fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 30 (±)-*cis*-7-[[4-(2-Methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-7-[[4-(2-Chlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 35 (±)-*cis*-1-Bromo-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
 (±)-*cis*-1-Methyl-7-[[4-(3-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;

(-)-*cis*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol, and;

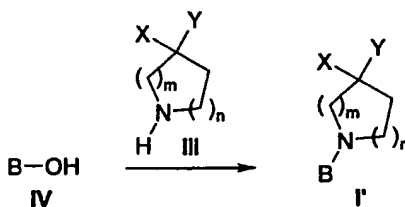
(-)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol.

- 5 In accordance with another aspect of the invention, there is provided a process for the preparation of a compound in accordance with the invention, which process comprises:-

- 1) where A in formula I is a bond (formula I'),  
 a). reacting a ketone of formula II with an amine of formula III under reductive  
 10 amination conditions, such as NaCNBH<sub>3</sub> in methanol or acetonitrile (Lane, *Synthesis*, 135, 1975),



- 15 wherein B, m, n, X and Y are as defined in formula I, or  
 b). transforming an alcohol of formula IV into a suitable leaving group (e.g. methanesulfonate, p-toluenesulfonate or bromide) and subsequent reaction with an amine of formula III,

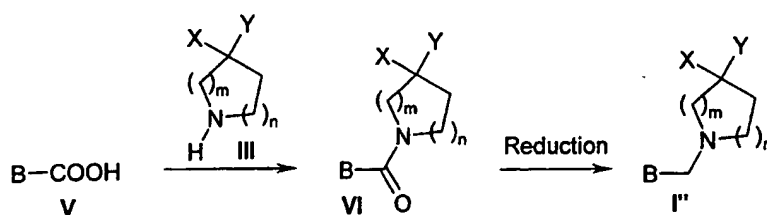


20

wherein B, m, n, X and Y are as defined in formula I; or

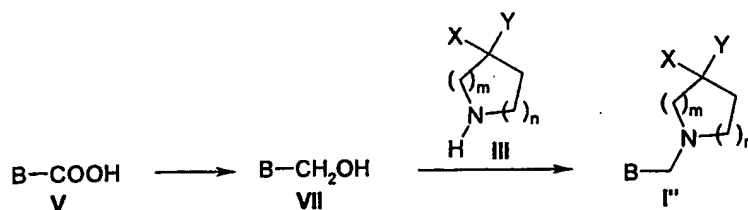
2) where A in formula I is a group  $-(CR_{pa}R_{pb})_p-$  and p is 1 and  $R_{pa}$  and  $R_{pb}$  are both hydrogen (formula I''),

- 25 c) reacting a carboxylic acid of formula V with an amine of formula III via formation of an acyl halide or by direct reaction with a coupling agent, such as dicyclohexylcarbodiimide/1-hydroxybenzotriazole, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide/1-hydroxybenzotriazole or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate, and thereafter reducing the  
 30 resulting amide of formula VI using a metal hydride or borane-based reagent,



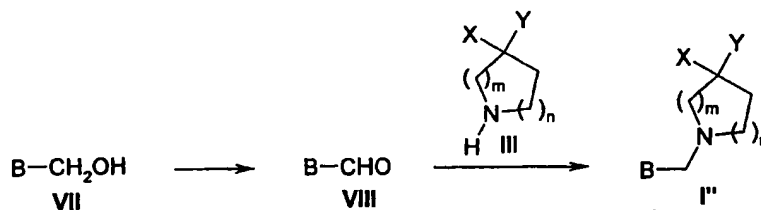
wherein B, m, n, X and Y are as defined in formula I, or

- 5 d) reducing a carboxylic acid of formula V to an alcohol of formula VII (Pelter Smith, Brown, *Borane Reagents*; Academic Press: London, 1988), and reacting said alcohol with an amine of formula III according to method b) above,



wherein B, m, n, X and Y are as defined in formula I, or

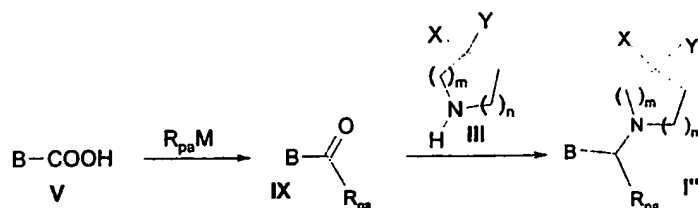
- e) oxidizing an alcohol of formula **VII** to an aldehyde of formula **VIII**, using for example  $\text{MnO}_2$ , PDC or DMSO/oxalyl chloride (Swern, *J. Org. Chem.*, **43**, 2480, 1978) and reacting said aldehyde with an amine of formula **III** under reductive amination conditions, according to method a) above,



wherein B, m, n, X and Y are as defined in formula I; or

- 20 3) where A in formula I is a group  $-(CR_{pa}R_{pb})_p-$  and p is 1,  $R_{pa}$  is a  $C_{1-6}$  alkyl group and  $R_{pb}$  is hydrogen (formula I'''),  
f) reacting a carboxylic acid or a derivative thereof of formula V with an organometallic compound of formula  $R_{pa}M$  wherein M represents a metal such as Li, Mg, Cu or Zn, e.g. alkyllithium derivatives, Grignard reagents, lithium  
25 dialkylcuprates or dialkylzinc derivatives (Trost, Fleming, *Comprehensive Organic*

Synthesis; Pergamon Press: Oxford, 1991; Vol. III), and thereafter reacting the resulting carbonylic compound IX with an amine of formula III under reductive amination conditions, according to method a) above,

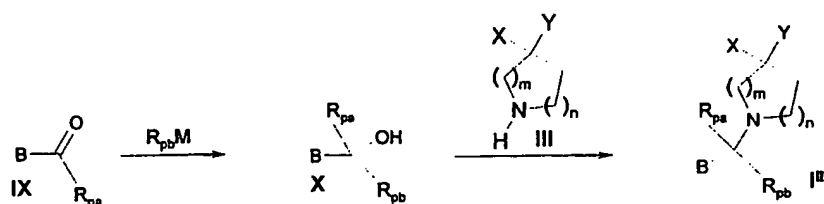


5

wherein B, R<sub>pa</sub>, m, n, X and Y are as defined in formula I; or

4) where A in formula I is a group -(CR<sub>pa</sub>R<sub>pb</sub>)<sub>p</sub>- and p is 1, and R<sub>pa</sub> and R<sub>2pb</sub> are both C<sub>1-6</sub> alkyl groups (formula I'''),

10 g) reacting a carbonylic compound of formula IX with an organometallic of formula R<sub>pb</sub>M, wherein M represents a metal such as Li or Mg, e.g. alkyllithium derivatives or Grignard reagents, and coupling the resulting alcohol of formula X with an amine of formula III according to method b) above



15

wherein B, R<sub>pa</sub>, R<sub>pb</sub>, m, n, X and Y are as defined in formula I.

Compounds of formula II, IV and V are either known compounds or may be prepared from known compounds with known methods (Hacksell, *J. Med. Chem.*, 24, 429, 1981, Murthy, *Tetrahedron*, 38, 2831, 1982, Bowman, *Tetrahedron*, 48, 4027, 1992).

20

Compounds of formula III are either known compounds or may be prepared from known compounds with known methods (Comins, *J. Org. Chem.*, 47, 4315, 1982).

25

Said compounds in accordance with the invention may be prepared in the form of salts or hydrates.

Suitable salts are pharmaceutically acceptable salts.

Suitable hydrates are pharmaceutically acceptable hydrates.

Administration of a compound in accordance with the invention may be by way of oral, sublingual, transdermal or parenteral administration.

30



An effective amount of the compound of the invention will depend on factors such, for example, as the nature and severity of the disorder(s) being treated and on the weight of the mammal. However, a unit does will normally contain 0.1 to 50 mg, for example 0.5 to 10 mg, of the compound. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more usually 1 to 3 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 0.1 to 50 mg, for example 0.1 to 5 mg, that is in the range of approximately 0.001 to 1mg/kg/day, more usually 0.005 to 0.2 mg/kg/day.

For oral or parenteral administration, it is greatly preferred that the compound is administered in the form of a unit dose composition, such as a unit dose oral or parenteral composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral preparations, powders, granules, lozenges, reconstitutable powders, injectable and liquid infusible solutions or suspensions or suppositories.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers include cellulose, mannitol, lactose and other similar agents.

Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycolate.

Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or

sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms may be prepared containing the compound and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition may be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound may be suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent may be included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the treatment concerned.

Accordingly, in yet another aspect of the present invention there is also provided a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable hydrate thereof, and a pharmaceutically acceptable carrier.

#### Preparation 1

##### (±)-4-Oxo-1,2,3,4-tetrahydro-2-naphthoic acid

100 mL (0.425 mol) of diethyl benzylmalonate were added dropwise to a stirred suspension of 28 g (0.7 mol) of NaH (60% dispersion in mineral oil) in 550 mL of absolute ethanol at room temperature. The reaction mixture was refluxed 2 h, then cooled to 50°C and 47.1 mL (0.425 mol) of ethyl bromoacetate were added dropwise. The reaction mixture was refluxed 2 h, then quenched with 150 mL of water; a solution of 140 g (3.5 mol) of NaOH in 400 mL of water was added and the mixture was heated to reflux for 1h. EtOH was removed *in vacuo*, the aqueous solution was washed with Et<sub>2</sub>O and then carefully brought to acidic pH with 350 mL of 37% HCl and extracted with AcOEt. The solvent was removed *in vacuo* and the resulting residue was heated to 180°C for 30 min. After cooling to room temperature, 100 mL of 95% H<sub>2</sub>SO<sub>4</sub> were added and the reaction mixture stirred for 2 h, then it was poured onto 500 g of crushed ice and extracted with Et<sub>2</sub>O. The organic phase was dried and the solvent removed *in vacuo*. The resulting residue was taken up in Et<sub>2</sub>O, washed with 40% NaOH solution then brought to acidic pH with 37% HCl and

extracted with Et<sub>2</sub>O. The organic phase was dried and the solvent removed *in vacuo*. The resulting solid residue was triturated with Et<sub>2</sub>O, filtered and dried yielding 15 g of the title compound, used without further purification. m.p. = 146-147°C. IR (cm<sup>-1</sup>): 2924, 1692, 1600; NMR (300 MHz, DMSO,  $\delta$  ppm): 12.6-12.5 (bs, 1H); 7.9 (d, 1H); 7.6-7.5 (m, 1H); 7.4-7.3 (m, 2H); 3.3-3.1 (m, 3H); 2.7 (m, 2H). MS (m/z): 191.1 (MH<sup>+</sup>).

### Preparation 2

#### (R)-(-)-4-Oxo-1,2,3,4-tetrahydro-2-naphthoic acid

A solution of 7.436 g (55 mmol) of (-)- $\alpha$ -ethylbenzylamine in 100 mL of MeOH was added to a solution of 10.5 g (55 mmol) of ( $\pm$ )-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid in 100 mL of MeOH. The solvent was removed *in vacuo*, and the residue was dissolved in 200 mL of AcOEt. The less soluble diastereoisomeric salt crystallised on standing. The salt was then recrystallised from AcOEt up to a constant optical activity, yielding 3.5 g of salt, which was transformed into the free acid by dissolving it in 6N HCl, extracting with Et<sub>2</sub>O and evaporating the solvent, yielding 2 g of the title compound.  $[\alpha]^{20}_D = -39.3$  (c = 1.5, MeOH). IR, NMR and m.p. matched those of the racemate.

### Preparation 3

#### (S)-(+)-4-Oxo-1,2,3,4-tetrahydro-2-naphthoic acid

The mother liquors obtained from the first crystallisation of Preparation 2 were evaporated to dryness. The residue was dissolved in 6N HCl, extracted with Et<sub>2</sub>O and evaporated to dryness, yielding 5.34 g of free acid which were treated with 3.79 g of (+)- $\alpha$ -ethylbenzylamine and worked up as described in Preparation 2, yielding 1.8 g of the title compound.  $[\alpha]^{20}_D = +39.48$  (c = 1.5, MeOH). IR, NMR and m.p. matched those of the racemate.

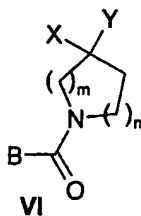
### Preparation 4

#### 2,3-Dihydro-2-[(4-phenylpiperidin-1-yl)carbonyl]-1H-indene

750 mg (4.6 mmol) of 2,3-dihydro-1H-inden-2-carboxylic acid (prepared as described in Hacksell, *J. Med. Chem.*, **24**, 429, 1981) were dissolved in 15 mL of CH<sub>2</sub>Cl<sub>2</sub> and 0.65 mL (7.4 mmol) of oxalyl chloride were added dropwise at 0°C under a nitrogen atmosphere. The solution was allowed to warm to room temperature in 2 h, then the solvent was removed *in vacuo*. The resulting acyl chloride was dissolved in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and added to a solution of 909 mg (4.6 mmol) of 4-phenylpiperidine hydrochloride and 1.9 mL (13.8 mmol) of triethylamine in 15 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0°C. The reaction mixture was allowed to warm to room temperature overnight, then water was added and the organic phase was

washed with 5% HCl and dried. The solvent was removed *in vacuo* and the resulting crude product was purified by flash chromatography, eluting with a mixture Et<sub>2</sub>O/Petroleum ether 7:3, yielding 630 mg of the title compound. IR (cm<sup>-1</sup>) = 2944, 1636, 1494. NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 7.35 (m, 2H); 7.25-7.1 (m, 7H); 4.85 (m, 1H); 4.15 (m, 1H); 3.55 (m, 1H); 3.4-3.3 (m, 2H); 3.3-3.1 (m, 3H); 2.85-2.6 (m, 2H); 2.0-1.9 (m, 2H); 1.75-1.6 (m, 2H). MS (m/z): 306.0 (MH<sup>+</sup>).

Compounds of formula VI and described in Table 1 were obtained following the procedure described in Preparation 4.



5

Table 1

Prep n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	MS (m/z) (MH <sup>+</sup> )	[α] <sub>D</sub> <sup>20</sup>
5	(±)-3-[(4-Phenylpiperidin-1-yl)carbonyl]-1-oxo-2H-3,4-dihydronaphthalene		Ph	H	2	1	118-119	2934, 1688, 1642	334.3	-
6	(S)-(+)-3-[(4-Phenylpiperidin-1-yl)carbonyl]-1-oxo-2H-3,4-dihydronaphthalene		Ph	H	2	1	118-120	2930, 1688, 1642	334.4	+43.2 c=1, MeOH
7	(R)-(-)-3-[(4-Phenylpiperidin-1-yl)carbonyl]-1-oxo-2H-3,4-dihydronaphthalene		Ph	H	2	1	118-119	2930, 1688, 1644	334.4	-41.2 c=1, MeOH
8	(±)-2-[(4-Phenylpiperidin-1-yl)carbonyl]-1,2,3,4-tetrahydronaphthalene		Ph	H	2	1	90-91	2926, 1626, 1442	320.2	-
9	(±)-1,2-Dihydro-2-[(4-phenylpiperidin-1-yl)carbonyl]phenanthren-4-(3H)-one		Ph	H	2	1	-	-	-	-

**Preparation 10****(±)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one-7-carboxylic acid**

A suspension of 0.7 g (3 mmol) of ethyl (±)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one-7-carboxylate (prepared as described in Bowman, *Tetrahedron*, 48, 4027, 1992) in 2 mL of 2N NaOH (4 mmol) was refluxed for 2 h, then cooled and extracted with Et<sub>2</sub>O. The aqueous layer was brought to acidic pH with 10% HCl, the precipitate formed was redissolved in Et<sub>2</sub>O and the organic phase was washed with water and dried. The solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography, eluting with a mixture of CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 respectively, yielding 0.41 g of the title compound. m.p. = 134-135°C.

**Preparation 11****(±)-7-[(4-Phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one**

To a solution of 0.3 g (1.47 mmol) of (±)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one-7-carboxylic acid in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> were added, at 0°C, 0.27 mL (3.69 mmol) of SOCl<sub>2</sub> and the solution was warmed at 50°C for 20 min. The solvent and the excess SOCl<sub>2</sub> were removed *in vacuo* and the resulting residue was redissolved in 5 mL of CH<sub>2</sub>Cl<sub>2</sub>. 0.24 g (1.47 mmol) of 4-phenylpiperidine and 0.2 mL (1.47 mmol) of triethylamine dissolved in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> were added at room temperature to this solution; the stirring was continued overnight, then the solvent was removed *in vacuo* and the residue was taken up in AcOEt; the organic phase was washed successively with 10% NaOH, 10% HCl and water, the solvent was removed *in vacuo* yielding 0.49 g of the title compound as an oil which was used without further purification.

**Preparation 12****2-Methylphenethyl alcohol methanesulfonate**

10 g (0.0734 mol) of 2-methylphenethyl alcohol were dissolved in 200 mL of dry CH<sub>2</sub>Cl<sub>2</sub> under a nitrogen atmosphere; the solution was cooled to 5°C, 16.4 mL (0.1175 mol) of triethylamine were added, followed by a solution of 9.1 mL (0.1175 mol) of methanesulfonyl chloride in 100 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, keeping the temperature below 15 °C. The reaction mixture was allowed to warm to room temperature in 2 h, then 250 mL of water were added, the organic phase was collected and the solvent was removed *in vacuo*. The resulting oil was taken up in Et<sub>2</sub>O and washed with 1N HCl and successively with saturated NaHCO<sub>3</sub> solution, the solvent was removed *in vacuo*, yielding 14.5 g of the title product which was used without further purification.

IR,  $^1\text{H}$  nmr spectra and mass spectra were consistent with the assigned structure.

### Preparation 13

#### Diethyl (2-methyl)phenethyl malonate

5 33.9 mL (0.223 mol) of diethyl malonate were added, under a nitrogen atmosphere and at room temperature, to a solution of sodium ethoxide (prepared *in situ* by dissolving 2.6 g (0.0151 mol) of Na in 80 mL of absolute EtOH). After 30 min, 14.5 g (0.0677 mol) of 2-methylphenethyl alcohol methanesulfonate dissolved in 40 mL of abs. EtOH were added dropwise and the resulting solution was heated to reflux for  
10 3 h. EtOH was removed *in vacuo*, the residue was taken up in water and extracted with Et<sub>2</sub>O. The organic phase was washed successively with 10% HCl and brine, dried and the solvent was removed *in vacuo*. The excess diethyl malonate was removed by distillation under reduced pressure. The resulting oil (15.6 g) was used without further purification.

15 IR,  $^1\text{H}$  nmr spectra and mass spectra were consistent with the assigned structure.

### Preparation 14

#### Diethyl 2-(*t*-butoxycarbonylmethyl)-2-(2-methyl)phenethyl malonate

20 A solution of 7.7 g (0.0277 mol) of diethyl (2-methyl)phenethyl malonate in 70 mL of dry THF were added dropwise, under a nitrogen atmosphere at room temperature, to a suspension of 1.4 g (0.036 mol) of NaH (60% dispersion in mineral oil) in 160 mL of dry THF. The reaction mixture was stirred for 30 min, then 5.3 mL (0.036 mol) of *t*-butyl bromoacetate were added dropwise. After 3 h the reaction mixture was quenched with water (at 0°C) and extracted with Et<sub>2</sub>O. The organic phase was dried,  
25 the solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with a mixture Hexane/Et<sub>2</sub>O 8:2, yielding 9.3 g of the title compound.

IR,  $^1\text{H}$  nmr spectra and mass spectra were consistent with the assigned structure.

### 30 Preparation 15

#### Diethyl 2-carboxymethyl-2-(2-methyl)phenethyl malonate

18.7 g (0.0476 mol) of diethyl 2-(*t*-butoxycarbonylmethyl)-2-(2-methyl)phenethyl malonate were dissolved in 40 mL of trifluoroacetic acid and stirred 1 h at room temperature. Trifluoroacetic acid was removed *in vacuo*, the residue was taken up in  
35 water and extracted with Et<sub>2</sub>O. The organic phase was dried and the solvent was removed *in vacuo*, yielding 16.8 g of the title compound which was used without further purification.

IR,  $^1\text{H}$  nmr spectra and mass spectra were consistent with the assigned structure.

**Preparation 16****(±)-1-Methyl-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene-7-carboxylic acid**

16. 8 g (0.0499 mol) of diethyl 2-carboxymethyl-2-(2-methyl)phenethyl malonate were dissolved in 120 mL of CH<sub>2</sub>Cl<sub>2</sub> under a nitrogen atmosphere. The solution was cooled to 5°C and 19 mL (0.1498 mol) of oxalyl chloride were added dropwise. After 3 h the volatiles were removed *in vacuo*, the resulting oil was dissolved in 200 mL of CH<sub>2</sub>Cl<sub>2</sub> and this solution was added dropwise, at 0°C and under inert atmosphere, to a suspension of 26.6 g (0.1996 mol) of AlCl<sub>3</sub> in 300 mL of CH<sub>2</sub>Cl<sub>2</sub>. The resulting suspension was vigorously stirred overnight, during which time it was allowed to warm to room temperature. Water was added, followed by 1N HCl up to pH 1. The layers were separated, the organic phase was dried and the solvent was removed *in vacuo*. The resulting crude product was taken up in dioxane (60 mL) and 6N HCl (200 mL) and heated to reflux for 6 h. After cooling, water was added and the reaction mixture was extracted with Et<sub>2</sub>O. The organic phase was dried, the solvent was removed *in vacuo* and the resulting crude product was purified by flash chromatography eluting with Et<sub>2</sub>O, yielding 5.9 g of the title product. IR, <sup>1</sup>H nmr spectra and mass spectra were consistent with the assigned structure.

The following compounds were obtained according to procedures described in Preparations 12-16:

- (±)-1,3-Dimethyl-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene -7-carboxylic acid;
  - (±)-3-Chloro-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene -7-carboxylic acid;
  - (±)-1-Chloro-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene -7-carboxylic acid;
  - (±)-1-Fluoro-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene -7-carboxylic acid,
  - and;
  - (±)-1-Bromo-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene -7-carboxylic acid.
- IR, <sup>1</sup>H nmr spectra and mass spectra for all the above compounds were consistent with the assigned structures.

**Preparation 17****(±)-1-Methoxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene -7-carboxylic acid**

The title compound was obtained following procedure described in Preparation 10. IR and <sup>1</sup>H nmr spectra were consistent with the assigned structure.

**Preparation 18****(±)-4-Methoxy-5-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene -7-carboxylic acid**

The title compound was obtained following procedure assigned in Preparation 10.



IR and  $^1\text{H}$  nmr spectra were consistent with the assigned structure.

The following compounds were obtained according to procedure described in Preparation 4:

- ( $\pm$ )-1-Methyl-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
5 ( $\pm$ )-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
( $\pm$ )-1-Methyl-7-[[4-(3-fluorophenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
10 ( $\pm$ )-1-Methoxy-7-[[4-(2-methylphenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
( $\pm$ )-1-Methoxy-7-[[4-(3-fluorophenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
( $\pm$ )-1,3-Dimethyl-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
15 ( $\pm$ )-3-Chloro-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
( $\pm$ )-1-Chloro-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
20 ( $\pm$ )-1-Fluoro-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
( $\pm$ )-1-Bromo-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
( $\pm$ )-7-[[4-(2-Methoxyphenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
25 ( $\pm$ )-7-[[4-(3-Fluorophenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
( $\pm$ )-7-[[4-(2-Methylphenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
30 ( $\pm$ )-7-[[4-(4-Benzyloxyphenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
( $\pm$ )-7-[[4-(3-Bromophenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
( $\pm$ )-7-[[4-(4-Fluorophenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
35 ( $\pm$ )-7-[[4-(3,5-Dimethoxyphenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;  
( $\pm$ )-7-[[4-(2-Chlorophenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;

(±)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one, and;  
(±)-4-Methoxy-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one.

5 IR, <sup>1</sup>H nmr spectra and mass spectra for all the above compounds were consistent with the assigned structures.

#### Preparation 19

10 (±)-1-Phenyl-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one

0.6 g (1.54 mmol) of (±)-1-bromo-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one were dissolved in 5 mL of toluene under a nitrogen atmosphere, then 54 mg (0.016 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub> were added, followed by 1.5 mL of 2M Na<sub>2</sub>CO<sub>3</sub> solution and 225 mg (1.85 mmol) of benzenboronic acid  
15 dissolved in 2 mL of MeOH. The resulting heterogeneous mixture was refluxed for 8 h under vigorous stirring, then after cooling it was taken up with CH<sub>2</sub>Cl<sub>2</sub> and water. 8 mL of 2M Na<sub>2</sub>CO<sub>3</sub> solution and 1 mL of conc. NH<sub>4</sub>OH were added, the organic layer was collected and dried, the solvent was removed *in vacuo*, yielding 660 mg of the title product which was used without further purification.

20 IR, <sup>1</sup>H nmr spectra and mass spectra were consistent with the assigned structure.

#### Preparation 20

(±)-1-Hydroxy-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one

25 Under a nitrogen atmosphere, 2.2 mL (0.0234 mol) of BBr<sub>3</sub> were added to 20 mL of CH<sub>2</sub>Cl<sub>2</sub>, then 1.47 g (0.0039 mol) of (±)-1-methoxy-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one dissolved in 25 mL of CH<sub>2</sub>Cl<sub>2</sub> were added dropwise at room temperature. The reaction mixture was stirred for 2 h, then it was poured onto 25 g of crushed ice, basified with conc. NH<sub>4</sub>OH and  
30 extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried and the solvent was removed *in vacuo*. The resulting crude solid was triturated with Et<sub>2</sub>O, filtered and dried, yielding 1.16 g of the title product.

IR, <sup>1</sup>H nmr spectra and mass spectra were consistent with the assigned structure.

#### 35 Preparation 21

(±)-1-Benzoyloxy-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one

600 mg (0.00165 mol) of (±)-1-hydroxy-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one were dissolved in 100 mL of abs.

EtOH under a nitrogen atmosphere, then 228 mg (0.00165 mol) of anhydrous  $K_2CO_3$  and a catalytic amount of KI were added, followed by 0.216 mL (0.0018 mol) of benzylbromide. The reaction mixture was stirred 3h at room temperature, then 0.216 mL of benzylbromide were added and the stirring continued overnight. Further 0.216 mL of benzylbromide was added and the reaction stirred overnight. The solvent was then evaporated, the residue was taken up in water, brought to pH 1 with 1N HCl and extracted with AcOEt. The organic phase was dried and the solvent was removed *in vacuo*, the resulting crude product was purified by flash chromatography, eluting with a mixture  $Et_2O$ /Hexane 8:2 respectively, yielding 595 mg of the title compound.

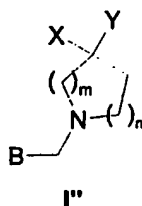
IR,  $^1H$  nmr spectra and mass spectra were consistent with the assigned structure.

#### Example 1

**2,3-Dihydro-2-[(4-phenylpiperidin-1-yl)methyl]indene hydrochloride**

630 mg (2.06 mmol) of 2,3-dihydro-2-[(4-phenylpiperidin-1-yl)carbonyl]-1H-indene dissolved in 10 mL of dry THF were added dropwise to a suspension of 300 mg of  $LiAlH_4$  in 40 mL of dry THF at room temperature. The reaction mixture was stirred 2 h, then it was quenched by sequential addition of 0.35 mL of water, 1 mL of 15% NaOH and 0.35 mL of water and stirred for 90 min. The resulting precipitate was filtered by suction and the filtrate was evaporated to dryness. The resulting residue was dissolved in THF, brought to acidic pH with  $Et_2O/HCl$  and the solvent was removed *in vacuo*. The resulting solid was triturated with hot acetone, filtered and dried, yielding 370 mg of the title compound. m.p. > 240°C. IR ( $cm^{-1}$ ) = 2930, 2376, 1478. NMR (300 MHz,  $CDCl_3$ ,  $\delta$  ppm): 7.30-7.10 (m, 1H); 3.10-3.02 (m, 4H); 2.80-2.69 (m, 3H); 2.55-2.41 (m, 1H); 2.42 (d, 2H); 2.12-2.02 (m, 2H); 1.86-1.78 (m, 4H). MS (m/z): 292 ( $MH^+$ ).

Compounds of formula I'' and described in Table 2 were obtained following procedure described in Example 1.



5

Table 2

Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (300 MHz) δ ppm	MS (m/z) (MH <sup>+</sup> )
2	(±)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-hydroxy-2H-3,4-dihydronaphthalene		Ph	H	2	1	107-108	3398, 2936, 1450	(CDCl <sub>3</sub> ): 7.51(d, 1H); 7.32-7.17(m, 7H); 7.09(d, 1H); 5.00-4.50(s br, 1H); 4.79(t, 1H); 3.11(dq, 1H); 2.98(dd, 1H); 2.90(dq, 1H); 2.59-2.44(m, 2H); 2.41-2.29(m, 3H); 2.23-2.01(m, 3H); 1.98-1.72(m, 5H).	322
3	(±)-2-[(4-Phenylpiperidin-1-yl)methyl]-1,2,3,4-tetrahydronaphthalene hydrochloride		Ph	H	2	1	264-265	3026, 2928, 1492	(CDCl <sub>3</sub> ): 12.40(s br, 1H); 7.32-7.05(m, 9H); 3.72(m, 2H); 3.15-2.67(m, 11H); 2.47(m, 1H); 2.31(m, 1H); 2.00(m, 2H); 1.74-1.61(m, 1H).	306

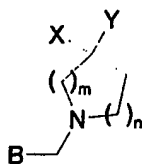
**Example 4**

10 **(±)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene hydrochloride**

1.5 g of activated MnO<sub>2</sub> were added to a stirred solution of 1.2 g of (±)-3-[(4-phenylpiperidin-1-yl)methyl]-1-hydroxy-2H-3,4-dihydronaphthalene in 20 mL of AcOEt. The stirring was continued for 7 days, then the resulting mixture was filtered  
 15 and the filtrate evaporated to dryness. The crude product was purified by column

- chromatography, eluting with a mixture hexane/AcOEt 9:1 respectively, yielding 0.7 g of free base which was dissolved in Et<sub>2</sub>O, brought to acidic pH with Et<sub>2</sub>O/HCl and evaporated to dryness. The resulting solid was triturated with Et<sub>2</sub>O, filtered and dried, yielding 0.65 g of the title compound. m.p. 261-262 °C. IR (cm<sup>-1</sup>) = 3028, 2934, 1678. NMR: (300 MHz, CDCl<sub>3</sub>, δ ppm): 8.03 (dd, 1H); 7.49 (dt, 1H); 7.33-7.18 (m, 7H); 3.12 (d, 1H); 3.03-2.92 (m, 2H); 2.86 (d, 1H); 2.75 (dd, 1H); 2.55-2.30 (m, 5H); 2.16-2.02 (m, 2H); 1.84-1.76 (m, 4H). MS (m/z): 320 (MH<sup>+</sup>)
- 5

Compounds of formula I'' and described in Table 3 were obtained following procedure described in Example 4.



I''  
Table 3

Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (300 MHz) δ ppm	MS (m/z) (MH <sup>+</sup> )	[α] <sub>D</sub> <sup>20</sup>
5	(R)-(-)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene hydrochloride		Ph	H	2	1	259-260	3028, 2934, 1678	(CDCl <sub>3</sub> ): 8.03(dd, 1H); 7.49(dt, 1H); 7.33-7.18(m, 7H); 3.12(d, 1H); 3.03-2.92(m, 2H); 2.86(d, 1H); 2.75(dd, 1H); 2.55-2.30(m, 5H); 2.16-2.02(m, 2H); 1.84-1.76(m, 4H).	320	-11.30 c=0.5, MeOH
6	(S)-(+)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene hydrochloride		Ph	H	2	1	257-258	3030, 2930, 1678	(CDCl <sub>3</sub> ): 8.03(dd, 1H); 7.49(dt, 1H); 7.33-7.18(m, 7H); 3.12(d, 1H); 3.03-2.92(m, 2H); 2.86(d, 1H); 2.75(dd, 1H); 2.55-2.30(m, 5H); 2.16-2.02(m, 2H); 1.84-1.76(m, 4H).	320	+11.74 c=0.5, MeOH
7	(±)-1,2-Dihydro-2-[(4-phenylpiperidin-1-yl)methyl]phenanthren-4-(3H)-one hydrochloride		Ph	H	2	1	-	-	-	-	-

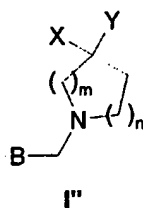
**Example 8****(±)-2-[(4-Phenylpiperidin-1-yl)methyl]-1,2-dihydronaphthalene hydrochloride**

- 5 0.5 g of (±)-3-[(4-phenylpiperidin-1-yl)methyl]-1-hydroxy-2H-3,4-dihydronaphthalene were dehydrated with Et<sub>2</sub>O/HCl at room temperature, yielding 0.3 g of the title compound. m.p. = 239-240°C; IR (cm<sup>-1</sup>) = 2932, 2604, 1494. NMR: (300 MHz, DMSO, 353K, as a base, δ ppm): 7.30-7.02 (m, 9H); 6.46 (d, 1H); 6.00 (dd, 1H); 2.89 (m, 2H); 2.65 (m, 2H); 2.40 (m, 2H); 2.10 (m, 4H); 1.80-1.60 (m, 4H). MS (m/z): 304 (MH<sup>+</sup>).
- 10

**Example 9****(±)-cis-7-[(4-Phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol**

- 15 0.15 g (3.8 mmol) of LiAlH<sub>4</sub> were added to a solution of 0.33 g (0.95 mmol) of (±)-7-[(4-phenylpiperidin-1-yl)carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one in 15 mL of dry Et<sub>2</sub>O at 0°C and the resulting mixture was heated to reflux overnight. After cooling, the reaction was quenched by the careful addition of 0.5 mL of 2 N NaOH, the suspension was stirred 10 min and then filtered by suction on a Celite pad washing with Et<sub>2</sub>O. The solvent was removed *in vacuo*, yielding 0.25 g
- 20 of the title compound. m.p. = 48-50°C.

Compounds of formula I'' and described in Table 4 were obtained following procedure described in Example 9.



5

Table 4

Ex n°	Name	B	X	Y	m	n	m.p. (°C)
10	(±)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		Ph	H	2	1	46-48
11	(±)-3-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		Ph	H	2	1	45-48

**Example 12**

10 **(±)-7-[(4-Phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride**

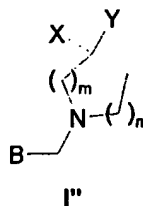
0.17 mL of the Jones reagent (prepared by mixing 2.67 g of CrO<sub>3</sub> and 2.3 mL of conc. H<sub>2</sub>SO<sub>4</sub> and adding water up to a final volume of 10 mL) were added to a solution of 0.2 g (0.6 mmol) of (±)-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol in 13 mL of acetone. The solution was stirred at room temperature for 1 h, then the solvent was removed *in vacuo*, the residue was taken up in water, brought to basic pH with 10% NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried and the solvent was removed *in vacuo*, obtaining 0.15 g of an oil which was dissolved in Et<sub>2</sub>O and brought to acidic pH with Et<sub>2</sub>O/HCl. The resulting white solid was triturated with Et<sub>2</sub>O, filtered and dried, yielding 0.1 g of the title compound. m.p. = 220°C (dec.).

15

20



Compounds of formula I'' and described in Table 5 were obtained following procedure described in Example 12.



5

Table 5

Ex. n°	Name	B	X	Y	m	n	m.p. (°C)
13	(±)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride		Ph	H	2	1	140-143
14	(±)-3-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride		Ph	H	2	1	185-188

**Example 15**

10 **(±)-cis-5-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene hydrochloride**

A solution of 0.1 g (0.3 mmol) of (±)-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol in 2 mL of MeOH and 0.05 mL of conc. H<sub>2</sub>SO<sub>4</sub> was refluxed overnight. After cooling, the solvent was removed *in vacuo*, the residue was taken up in 10% NaOH and extracted with AcOEt. The organic phase was washed with water, dried and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography, eluting with a mixture CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 respectively, obtaining the *cis* diastereoisomer as the faster eluting compound. The compound was dissolved in Et<sub>2</sub>O and brought to acidic pH with Et<sub>2</sub>O/HCl. The resulting white solid was triturated with Et<sub>2</sub>O, filtered and dried,

15

20

yielding 0.03 g of the title compound. m.p. = 213-215°C. NMR: (300 MHz, CDCl<sub>3</sub>, as a base,  $\delta$  ppm): 7.47 (d, 1H); 7.30-7.10 (m, 8H); 4.38 (d, 1H); 3.49 (s, 3H); 2.98 (m, 2H); 2.84-2.70 (m, 2H); 2.53-2.41 (m, 1H); 2.30 (dd, 1H); 2.20-1.95 (m, 6H); 1.85-1.73 (m, 4H); 1.20 (dd, 1H); 1.00-1.89 (m, 1H).

5

#### Example 16

##### ( $\pm$ )-*trans*-5-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene hydrochloride

The chromatography of the preceding example was continued, obtaining the *trans* diastereoisomer as the slower eluting compound. The compound was dissolved in Et<sub>2</sub>O and brought to acidic pH with Et<sub>2</sub>O/HCl. The resulting white solid was triturated with Et<sub>2</sub>O, filtered and dried, yielding 0.02 g of the title compound. (m.p. = 220-222°C). NMR: (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 7.30-7.10 (m, 9H); 4.35 (d, 1H); 3.20 (s, 3H); 3.20 (d, 1H); 3.01 (m, 2H); 2.65 (m, 1H); 2.55-2.30 (m, 3H); 2.20-1.95 (m, 5H); 1.80 (m, 4H); 1.31 (dt, 1H); 1.01 (dt, 1H).

15

#### Example 17

##### 1-(2,3-Dihydro-1H-inden-2-yl)-4-phenylpiperidine hydrochloride

190 mg (3 mmol) of NaCNBH<sub>3</sub> were added portionwise at room temperature to a stirred solution of 200 mg (1.5 mmol) of 2-indanone, 490 mg (3 mmol) of 4-phenylpiperidine and 0.35 mL (6 mmol) of glacial acetic acid in 20 mL of MeOH. After stirring overnight, the solvent was removed *in vacuo* and the residue was taken up in water, brought to basic pH with 10% NaOH and extracted with AcOEt. The organic phase was dried and the solvent removed *in vacuo*; the resulting crude product was purified by flash chromatography, eluting with a mixture n-hexane/AcOEt 8:2 respectively. The compound was dissolved in Et<sub>2</sub>O and brought to acidic pH with Et<sub>2</sub>O/HCl. The solvent was removed *in vacuo* and the product was crystallised from (i-Pr)<sub>2</sub>O, yielding 190 mg of the title compound. m.p. > 250°C. IR (cm<sup>-1</sup>) = 2927, 2444, 1469. NMR: (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 7.30-7.10 (m, 9H); 3.29-3.09 (m, 5H); 2.96 (dd, 2H); 2.59-2.49 (m, 1H); 2.21-2.11 (m, 2H); 1.90-1.80 (m, 4H). MS (m/z): 278 (MH<sup>+</sup>).

30

#### Example 18

##### N-(6,7,8,9-Tetrahydro-5H-benzocyclohepten-7-yl)-4-phenylpiperidine hydrochloride

35

The title compound was obtained according to the method described in Example 17, starting from 3-benzosuberone (prepared as described in Ewing, *J. Org. Chem.*, 40, 2965, 1975). m.p. > 250°C. IR (KBr, cm<sup>-1</sup>): 2940, 2466, 1455. NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 7.32-7.19 (m, 9H); 2.93-2.78 (m, 7H); 2.48-2.39 (m, 3H); 2.20-2.10

(m, 2H); 1.88-1.68 (m, 4H); 1.45 (dt, 2H). MS (m/z): 306 (MH<sup>+</sup>).

#### Example 19

(±)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride

- 5 729 mg (1.94 mmol) of (±)-1-methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]carbonyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one dissolved in 20 mL of dry THF were added dropwise, at 0°C and under a nitrogen atmosphere, to a suspension of 300 mg of LiAlH<sub>4</sub> in 15 mL of dry THF. The reaction mixture was
- 10 allowed to warm to room temperature then heated at 60°C for 3 h. After cooling, it was quenched by adding, at 0°C, 0.3 mL H<sub>2</sub>O, 1 mL 15% NaOH and 0.3 mL H<sub>2</sub>O. After stirring for 1 h, the resulting precipitate was filtered by suction and the filtrate was evaporated to dryness. The resulting residue was purified by flash chromatography, eluting with a mixture CH<sub>2</sub>Cl<sub>2</sub>/MeOH/conc. NH<sub>4</sub>OH 100:3:0.3
- 15 respectively, yielding 319 mg of compound, which was dissolved in Et<sub>2</sub>O, brought to acidic pH with Et<sub>2</sub>O/HCl and the solvent was removed *in vacuo*. The resulting solid was triturated with hot acetone, filtered and dried, yielding 290 mg of the title compound. m.p. >250°C. IR (KBr, cm<sup>-1</sup>) = 3248, 2924, 1463. NMR: (300 MHz, CDCl<sub>3</sub>, δ ppm): 7.43 (d, 1H); 7.25 (d, 1H); 7.21-7.05 (m, 5H); 5.02 (d, 1H); 3.03 (dd, 1H); 3.00 (m, 2H); 2.75-2.64 (m, 1H); 2.47 (dd, 1H); 2.33 (s, 6H); 2.25 (d, 1H);
- 20 2.19-2.00 (m, 4H); 2.13 (s, 2H); 1.88-1.70 (m, 4H); 1.35 (m, 1H); 0.89 (m, 1H). MS (m/z): 363 (M<sup>+</sup>); 188;

Compounds of formula I'' and described in Table 6 were obtained following procedure described in Example 19.

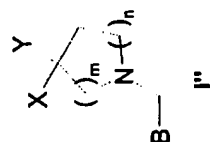
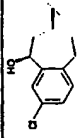
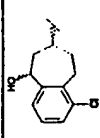
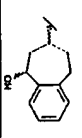
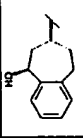


Table 6

Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
20	(±)-1,3-dimethyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		Ph	H	2	1	52-55	IR and <sup>1</sup> H nmr spectra were consistent with the assigned structure.		
21	(±)-cis-7-[[4-(2-methoxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		(2-OMe)Ph	H	2	1	72-74	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		

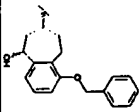
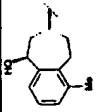
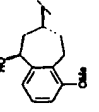
Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
22	(±)-cis-3-chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		Ph	H	2	1	-	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		
23	(±)-1-chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		Ph	H	2	1	-	(KBr); 3290, 1580, 1455.	(200 MHz, CDCl <sub>3</sub> ): 7.5 (d, 1H); 7.4-7.1 (m, 7H); 5.0 (d, 1H); 3.6-3.4 (m, 1H); 3.1-2.9 (m, 2H); 2.8-2.6 (m, 3H); 2.3-1.9 (m, 7H); 1.9-1.7 (m, 5H).	-
24	(±)-7-[(4-(2-hydroxyphenyl)piperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		(2-OH)Ph	H	2	1	158-160	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		
25	(±)-cis-7-[(4-(3-fluorophenyl)piperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		(3-F)Ph	H	2	1	238-240	(KBr); ; 3295, 2925, 1588.	(300 MHz, CDCl <sub>3</sub> , +D <sub>2</sub> O + Na <sub>2</sub> CO <sub>3</sub> , 333 K): 7.49 (d, 1H); 7.19-7.09 (m, 2H); 7.02-6.89 (m, 3H); 6.81 (d, 1H); 6.75 (dd, 1H); 4.82 (d, 1H); 2.89 (m, 2H); 2.75-2.60 (m, 2H); 2.48 (m, 2H); 2.48-2.34 (m, 1H); 2.15-1.90 (m, 6H); 1.75-1.61 (m, 4H); 1.20 (dt, 1H); 0.90-0.80 (m, 1H).	353 (M <sup>+</sup> ); 192; 149

Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
26	(±)-cis-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		(2-Me)Ph	H	2	1	>250	(KBr) ; 3293; 2926; 1454.	(300 MHz, CDCl <sub>3</sub> ): 7.59 (d, 1H); 7.25-7.04 (m, 7H); 4.99 (d, 1H); 3.00 (dd, 2H); 2.89-2.65 (m, 3H); 2.32 (s, 3H); 2.27 (d, 1H); 2.18-2.01 (m, 6H); 1.88-1.70 (m, 4H); 1.35 (dt, 1H); 0.99 (dt, 1H).	349 (M <sup>+</sup> ); 188; 117
27	(±)-cis-7-[[4-(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		Ph	H	2	1	52-55	(KBr) ; 3293; 1540; 1454.	(200 MHz, CDCl <sub>3</sub> ): 7.5-7.0 (m, 8H); 5.05 (d, 1H); 3.2-2.9 (m, 2H); 2.6-2.3 (m, 2H); s, 3H; 2.3-1.9 (m, 8H); 1.9-1.5 (m, 7H).	-
28	(±)-cis-7-[[4-(4-benzyloxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		(4-OBn)Ph	H	2	1	225-228	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		

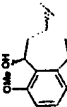
Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
29	(±)- <i>cis</i> -7-[[4-(3-bromophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		(3-Br)Ph	H	2	1	>250	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		
30	(±)-1-fluoro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		Ph	H	2	1	218-220			
31	(±)-7-[[4-(4-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		(4-F)Ph	H	2	1	227-229			
								(KBr) ; 3338; 2927; 1463.	(300 MHz, CDCl <sub>3</sub> , 343 K): 7.36 (d, 1H); 7.31-7.14 (m, 6H); 6.91 (dd, 1H); 4.96(d, 1H); 3.39 (ddd, 1H); 2.99 (m, 2H); 2.56-2.46 (m, 1H); 2.40-2.21 (m, 2H); 2.20-2.05 (m, 6H); 1.88-1.79 (m, 4H); 1.39 (dt, 1H); 0.98 (dt, 1H).	353 (M <sup>+</sup> ); 174;
								(KBr) ; 3269; 2930; 1511.	(300 MHz, CDCl <sub>3</sub> ): 7.59 (d, 1H); 7.30-7.12 (m, 4H); 7.10 (dd, 1H); 6.99 (dd, 2H); 4.98 (d, 1H); 2.99 (m, 2H); 2.88-2.70 (m, 2H); 2.52-2.42 (m, 1H); 2.29-1.99 (m, 7H); 1.81-1.70 (m, 4H); 1.38 (dt, 1H); 0.99 (dt, 1H).	353 (M <sup>+</sup> ); 192

Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
32	(±)-7-[[4-(3,5-dimethoxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		(3,5-di-OMe)Ph	H	2	1	223-225	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		
33	(±)-cis-1-phenyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		Ph	H	2	1	245-246	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		
34	(±)-7-[[4-(2-chlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		(2-Cl)Ph	H	2	1	239-240	(KBr); 3291; 2928; 1441.	(300 MHz, CDCl <sub>3</sub> ): 7.58 (d, 1H); 7.35-7.09 (m, 7H); 4.98 (d, 1H); 3.07-2.85 (m, 3H); 2.89-2.70 (m, 2H); 2.30-2.03 (m, 6H); 1.88-1.60 (m, 5H); 1.38 (dt, 1H); 0.99 (dt, 1H).	369 (M <sup>+</sup> ); 208; 174
35	(±)-cis-1-bromo-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		Ph	H	2	1	220-224	(KBr); 3344; 2937; 1445.	(300 MHz, CDCl <sub>3</sub> ): 7.54 (d, 1H); 7.46 (d, 1H); 7.32-7.17 (m, 5H); 7.08 (dd, 1H); 5.01 (d, 1H); 3.55 (dd, 1H); 2.98 (m, 2H); 2.59 (dd, 1H); 2.55-2.43 (m, 1H); 2.25 (d, 1H); 2.13 (s, 2H); 2.13-2.00 (m, 4H);	413 (M <sup>+</sup> ); 174



Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
	hydrochloride								1.92-1.68 (m, 4H); 1.32 (m, 1H); 0.90 (m, 1H).	
36	(±)-1-benzoyloxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		Ph	H	2	1	198-202	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		
37	(±)-cis-1-methyl-7-[[4-(3-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		(3-F)Ph	H	2	1	241-243	(KBr); 3270; 2930; 1440.	(300 MHz, CDCl <sub>3</sub> ): 7.42 (d, 1H); 7.28-7.21 (m, 1H); 7.14 (dd, 1H); 7.06 (d, 1H); 7.00 (d, 1H); 6.96-6.84 (m, 2H); 5.40 (d, 1H); 3.12 (dd, 1H); 2.97 (m, 2H); 2.54-2.41 (m, 2H); 2.31 (s, 3H); 2.22 (d, 1H); 2.19-2.00 (m, 4H); 2.12 (s, 2H); 1.82-1.70 (m, 4H); 1.31 (m, 1H); 0.89 (m, 1H).	367 (M <sup>+</sup> ); 192
38	(±)-cis-1-methoxy-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		(2-Me)Ph	H	2	1	-	(KBr); 3300; 1540; 1463.	(200 MHz, CDCl <sub>3</sub> ): 7.3-7.1 (m, 6H); 6.8 (m, 1H); 5.0 (d, 1H); 3.8 (s, 3H); 3.5 (m, 1H); 3.1-2.9 (m, 2H); 2.9-2.6 (m, 1H); 2.35 (s, 3H); 2.3-1.9 (m, 9H); 1.9-1.7 (m, 4H); 1.35-1.2 (m, 1H); 0.9 (m, 1H).	-

Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
39	(±)- <i>trans</i> -1-methoxy-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		(2-Me)Ph	H	2	1	-	IR and <sup>1</sup> H nmr spectra were consistent with the assigned structure.		
40	(±)- <i>cis</i> -1-methoxy-7-[[4-(3-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		(3-F)Ph	H	2	1	-	IR and <sup>1</sup> H nmr spectra were consistent with the assigned structure.		
41	(±)- <i>trans</i> -1-methoxy-7-[[4-(3-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol		(3-F)Ph	H	2	1	-	(KBr); 3295; 1580; 1455.	(200 MHz, CDCl <sub>3</sub> ): 7.3-6.8 (m, 7H); 5.0 (d, 1H); 3.8 (s, 3H); 3.2 (m, 1H); 2.5 (m, 1H); 2.4-2.1 (m, 4H); 2.1-1.6 (m, 10 H); 0.9 (m, 1H).	-
42	(±)- <i>cis</i> -1-hydroxy-7-[[4-phenylpiperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		Ph	H	2	1	190-193	IR and <sup>1</sup> H nmr spectra were consistent with the assigned structure.		

Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
43	(±)-4-methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride		Ph	H	2	1	176- 189	IR and <sup>1</sup> H nmr spectra were consistent with the assigned structure.		

Compounds of formula I'' and described in Table 7 were obtained following procedure described in Example 12.

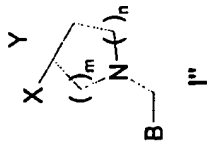


Table 7

Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
44	(±)-1,3-dimethyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride		Ph	H	2	1	222-225	IR and <sup>1</sup> H nmr spectra were consistent with the assigned structure.		

Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
45	(±)-7-[[4-(2-methoxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride		(2-OMe)Ph	H	2	1	232- 234	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		
46	(±)-3-chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride		Ph	H	2	1	180- 185	IR and <sup>1</sup> H nmr spectra were consistent with the assigned structure.		
47	(±)-1-chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride		Ph	H	2	1	-	IR and <sup>1</sup> H nmr spectra were consistent with the assigned structure.		

Ex n°	Name	B	X	Y	m	n	m.p. (°C)	IR (cm <sup>-1</sup> )	NMR (δ ppm)	MS (m/z)
48	(±)-7-[[4-(2-hydroxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride		(2-OH)Ph	H	2	1	216- 218	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		
49	(±)-1-methyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride		Ph	H	2	1	205- 210	(neat, free base): 2900; 1670; 1450.	(200 MHz, CDCl <sub>3</sub> ): 7.5 (d, 1H); 7.4-7.1 (m, 7H); 3.1-2.8 (m, 5H); 2.65-2.5 (m, 2H); 2.4 (s, 3H); 2.3-2.25 (m, 2H); 2.2-1.9 (m, 4H); 1.9-1.7 (m, 4H); 1.7-1.5 (m, 1H).	-
50	(±)-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride		(2-Me)Ph	H	2	1	202- 205	IR, <sup>1</sup> H nmr spectra and mass spectra were consistent with the assigned structure.		

**Example 51****(±)-7-[(4-phenylpiperidin-1-yl)methyl]-6,7-dihydro-5H-benzocycloheptene hydrochloride**

5 0.2 g (0.6 mmol) of (±)-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol were dissolved in 5 mL of 1,4-dioxane and 16 mL of 37% HCl and heated to reflux for 2 h. The reaction mixture was then basified with NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried and the solvent was removed *in vacuo*. The resulting crude product was purified by chromatography,  
10 eluting with a mixture CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:2 respectively; The compound was dissolved in Et<sub>2</sub>O and brought to acidic pH with Et<sub>2</sub>O/HCl. The resulting white solid was triturated with Et<sub>2</sub>O, filtered and dried, yielding 0.02 g of the title compound. m.p. = 268-270 °C.

15 IR, <sup>1</sup>H nmr spectra and mass spectra were consistent with the assigned structure.

**Example 52****7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene hydrochloride**

20 0.2 g of (±)-7-[(4-phenylpiperidin-1-yl)methyl]-6,7-dihydro-5H-benzocycloheptene were dissolved in 20 mL of MeOH, added to a suspension of 100 mg of 10% Pd-C in 5 mL of MeOH and hydrogenated at 50 psi for 6 h. The catalyst was filtered off, the solvent was removed *in vacuo* and the resulting crude product was purified by chromatography, eluting with a mixture CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:2 respectively. The  
25 compound was dissolved in Et<sub>2</sub>O and brought to acidic pH with Et<sub>2</sub>O/HCl. The resulting white solid was triturated with Et<sub>2</sub>O, filtered and dried, yielding 0.04 g of the title compound. m.p. >250 °C.

30 IR, <sup>1</sup>H nmr spectra and mass spectra were consistent with the assigned structure.

**Example 53****7-[[4-(2-Methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene hydrochloride**

The title compound was obtained as described in Examples 51 and 52 starting from  
35 (±)-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol. m.p. 245°C (dec.).

IR, <sup>1</sup>H nmr spectra and mass spectra were consistent with the assigned structure.

**Example 54**

**(±)-cis-5-Allyloxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene hydrochloride**

0.2 g (0.596 mmol) of (±)-cis-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol dissolved in 5 mL THF were added dropwise to a suspension of 0.029 g (0.715 mmol) of NaH (60% dispersion in mineral oil) in 10 mL THF. After 30 min at room temperature, 0.12 mL of allyl bromide were added and the reaction mixture was refluxed 8 h. After cooling, the reaction mixture was quenched by addition of MeOH and the solvent was removed *in vacuo*. The residue was taken up in 1 N NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>; the organic phase was dried and the solvent was removed *in vacuo*. The resulting crude product was purified by chromatography, eluting with a mixture CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:2 respectively, yielding an oil which was dissolved in Et<sub>2</sub>O; the solution was brought to acidic pH with Et<sub>2</sub>O/HCl and the solvent was removed *in vacuo*. The resulting solid was triturated with Et<sub>2</sub>O, yielding 65 mg of the title product. m.p. 126-128°C.

IR, <sup>1</sup>H nmr spectra and mass spectra were consistent with the assigned structure.

**Example 55**

**(±)-trans-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride**

0.7 g (2.1 mmol) of (±)-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one were dissolved in 40 mL of MeOH and 0.35 g of NaBH<sub>4</sub> were added portionwise. The reaction mixture was stirred 2 h at room temperature, the MeOH removed *in vacuo*, then the residue was taken up in 1N NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried and the solvent was removed *in vacuo*. The crude product was purified by chromatography, eluting with CH<sub>2</sub>Cl<sub>2</sub> and then with a mixture CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:3 respectively, yielding 100 mg of *trans* isomer which was dissolved in a mixture CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O: The solution was brought to acidic pH with Et<sub>2</sub>O/HCl and the solvent was removed *in vacuo*. The resulting solid was triturated with hot acetone, filtered and dried, yielding 90 mg of the title compound. m.p. >250°C.

IR, <sup>1</sup>H nmr spectra and mass spectra were consistent with the assigned structure.

**Example 56**

**(±)-cis-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride**



The diastereoisomeric mixture of Example 10 (150 mg) was chromatographed on silica gel by gradient elution starting from CH<sub>2</sub>Cl<sub>2</sub> up to a mixture CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:3 respectively, to yield the *cis* diastereoisomer as the faster eluting compound. The compound was dissolved in Et<sub>2</sub>O, the solution was brought to acidic pH with Et<sub>2</sub>O/HCl and the solvent was removed *in vacuo*. The resulting solid was trituated with hot acetone, filtered and dried, yielding 100 mg of the title compound. m.p. 229-231°C.

NMR (free base, 400 MHz, C<sub>6</sub>D<sub>6</sub>,  $\delta$  ppm): 7.49 (d, 1H); 7.24-7.02 (m, 6H); 6.60 (d, 1H); 4.75 (d, 1H); 3.79 (ddd, 1H); 3.41 (s, 3H); 2.75 (m, 2H); 2.34 (tt, 1H); 2.20 (m, 2H); 2.02 (m, 1H); 1.93-1.63 (m, 9H); 1.29 (dt, 1H); 0.84 (q br, 1H). MS (m/z): 366 (MH<sup>+</sup>); 348.

#### Example 57

##### ( $\pm$ )-*trans*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol hydrochloride

The chromatography of the preceding example was continued, obtaining the *trans* diastereoisomer as the slower eluting compound. The compound was dissolved in Et<sub>2</sub>O, the solution was brought to acidic pH with Et<sub>2</sub>O/HCl and the solvent was removed *in vacuo*. The resulting solid was trituated with hot acetone, filtered and dried, yielding 40 mg of the title compound. m.p. >250°C.

NMR (free base, 400 MHz, C<sub>6</sub>D<sub>6</sub>,  $\delta$  ppm): 7.21-7.03 (m, 6H); 6.88 (d, 1H); 6.60 (d, 1H); 4.79 (dd, 1H); 3.40 (m, 1H); 3.38 (s, 3H); 3.22 (ddd, 1H); 2.82 (m, 2H); 2.38 (m, 1H); 2.30 (m, 2H); 2.11 (m, 1H); 2.07 (d, 2H); 1.91-1.62 (m, 6H); 1.41 (ddd, 1H); 1.18 (dt, 1H). MS (m/z): 366 (MH<sup>+</sup>).

Racemic ( $\pm$ )-1-methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (compound of Example 13) was separated by preparative HPLC on chiral stationary phase (Daicel Chiracel OD, elution with 90:10:0.1 Hexane:Ethanol:Diethylamine, 12 mL/min), obtaining:

#### Example 58

##### (+)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride

The free base (e.e. >99% by HPLC) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, the solution was brought to acidic pH with Et<sub>2</sub>O/HCl and the solvent was removed *in vacuo*. The resulting solid was trituated with Et<sub>2</sub>O, filtered and dried, yielding the title compound.  $[\alpha]_D^{20} = +27.14$  (c = 0.1, MeOH). NMR (free base, 300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm): 7.30-7.15 (m, 7H); 7.00 (d, 1H); 3.84 (s, 3H); 3.16 (ddd, 1H); 3.00-2.80 (m, 4H); 2.59 (dd, 1H); 2.50-2.49 (m, 1H); 2.30 (m, 2H); 2.25-1.90 (m, 4H); 1.81-1.72 (m, 4H); 1.55 (m, 1H).

**Example 59**

**(-)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one hydrochloride**

- 5 The free base (e.e. = 96% by HPLC) was treated as described in the previous example, yielding the title compound.  $[\alpha]_D^{20} = -29.14$  (c = 0.1, MeOH).  $^1\text{H}$  NMR matched that of the opposite enantiomer.

- 10 Racemic ( $\pm$ )-*cis*-1-methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (compound of Example 56) was separated by preparative HPLC on chiral stationary phase (Daicel Chiracel OD, elution with 90:10:0.1 Hexane:Ethanol:Diethylamine, 12 mL/min), obtaining:

**Example 60**

- 15 **(+)-*cis*-1-methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol**

The title compound was obtained with e.e. = 98% (HPLC).  $[\alpha]_D^{20} = +64.2$  (c = 0.1, EtOH/Hexane).  $^1\text{H}$  NMR matched that of the racemate.

**Example 61**

- 20 **(-)-*cis*-1-methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol**

The title compound was obtained with e.e. = 96% (HPLC).  $[\alpha]_D^{20} = -65.8$  (c = 0.1, EtOH/Hexane).  $^1\text{H}$  NMR matched that of the racemate.

- 25 Racemic ( $\pm$ )-*trans*-1-methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (compound of Example 57) was separated by preparative HPLC on chiral stationary phase (Daicel Chiracel OD, elution with 90:10:0.1 Hexane:Ethanol:Diethylamine, 12 mL/min), obtaining:

**Example 62**

- 30 **(+)-*trans*-1-methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol**

The title compound was obtained with e.e. > 99% (HPLC).  $[\alpha]_D^{20} = +12.7$  (c = 0.5, EtOH).  $^1\text{H}$  NMR matched that of the racemate.

**Example 63**

- 35 **(-)-*trans*-1-methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol**

The title compound was obtained with e.e. > 97% (HPLC).  $[\alpha]_D^{20} = -12.1$  (c = 0.5, EtOH).  $^1\text{H}$  NMR matched that of the racemate.

**Example 64****[4-(2-Methylphenyl)-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-7-yl)]piperidine**

- 5 The title compound was obtained according to the method described in Example 17. IR, <sup>1</sup>H nmr spectra and mass spectra were consistent with the assigned structure.

- 10 Racemic (±)-*cis*-1-methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (compound of Example 19) was separated by preparative HPLC on chiral stationary phase (Daicel Chiracel OD, elution with 90:10:0.1 Hexane:Ethanol:Diethylamine, 12 mL/min), obtaining:

**Example 65****(-)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol**

- 15 The title compound was obtained with e.e. > 98% (HPLC).  $[\alpha]_D^{20} = -49$  (c = 0.1, EtOH/Hexane). <sup>1</sup>H NMR matched that of the racemate.

**Example 66****(+)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol**

- 20 The title compound was obtained with e.e. = 92% (HPLC).  $[\alpha]_D^{20} = +40$  (c = 0.1, EtOH/Hexane). <sup>1</sup>H NMR matched that of the racemate.

**Method of Nociceptin binding assay****25 Receptor cloning and expression**

- ORL-1 receptor was stably expressed in a Chinese Hamster Ovary (CHO) cell line (ACC-317) using a pCDN vector. Subclone selection was performed by growth in the absence of nucleosides. The cell line expressing high numbers of ORL-1 binding sites was selected for further characterization in radioligand binding and signal transduction assay (cAMP and GTPγS assays).
- 30

**Cell growth conditions**

- CHO cells are grown in suspension, in 1017 S03 culture and maintained at 37°C and 5%CO<sub>2</sub>. The cells are routinely grown on a shaker in the presence of 0.05% (v/v) pluronic acid (F68). The maximum cell density for this CHO cell lines is 4 x 10<sup>6</sup> cells/ml. The cultures are passed twice a week at a 1:5 or 1:10 dilution.
- 35

**Membrane preparation by hypotonic lysis**

All steps are performed at 4°C.

- 1) Harvest cells in PBS (approximately  $30 \times 10^6$  cells/tube). Collect cells by centrifugation (1200 rpm, ca 800x g 5 min).
- 2) Resuspend each pellet in 10 mM dibasic phosphate buffer, pH 7.2 (buffer A) - circa 30 ml/pellet. Centrifuge 15000 rpm 10 min (Sorvall SS-34 rotor).
- 5 3) Resuspend the pellets in the same volume of buffer A, incubate on ice for 20 min.  
Centrifuge at 1200 rpm, 5 min and save the supernatants.
- 4) Resuspend the low speed pellets in buffer A again and repeat step 3) two more times saving the supernatants each time.
- 10 5) Pool the low speed supernatants. Spin (15000 rpm, 10 min) to collect the membranes.
- 6) Resuspend the pellets in buffer A containing 0.32 M sucrose and 5 mM EDTA (buffer B). Pool, spin again at high speed to concentrate the membranes and wash in this storage buffer.
- 15 7) Resuspend in buffer B the final pellet to a final concentration of 5-10 mg protein/ml (ca  $10 \times 10^6$  cells/ml). Freeze the aliquots at - 80°C.

#### **Radioligand binding**

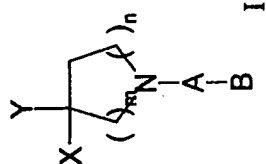
- 20 Radioligand binding experiments have been performed in Tris buffer pH 7.4 containing 100 ug/ml Bacitracine, 4 ug/ml Leupeptine and 2 ug/ml Chymostatine at the final volume of 1 ml, using [ $^3$ H]-Nociceptin (Amersham, 172 Ci/mmol) as the radioligand.

- Binding experiments were carried out at 25°C for 20 min and the reaction was terminated by filtration through Whatman GF/B filters pretreated with 0.2% PEI.
- 25 Filters were washed 3 times in Tris buffer pH 7.4 at 4 °C. The radioactivity present on the discs was measured by liquid scintillation counting using a 2500 Camberra Packard beta counter.

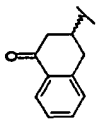
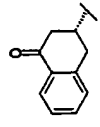
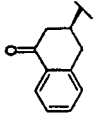
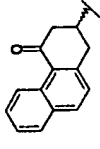
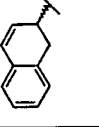
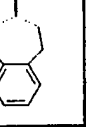
- 30 The most potent compounds in accordance with the present invention have an ORL-1 binding affinity ( $K_i$ ) in the range from 1 to 1000 nM.

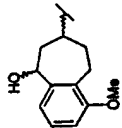
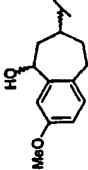
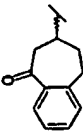
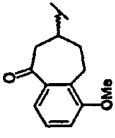
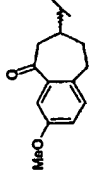
The stereochemistry shown for the Examples in the following Summary Table of Examples 1-66 serves to illustrate the relative stereochemistry of the compounds only.

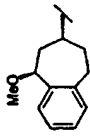
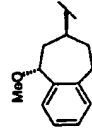


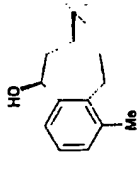
Summary Table of Examples 1-66



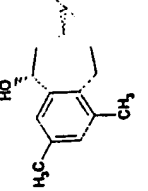
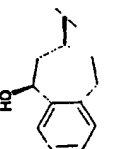
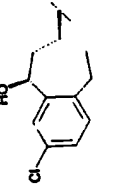
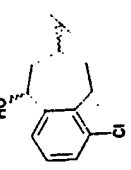
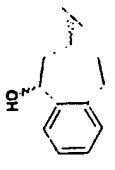
Example No.	X	Y	m	n	A	B	Molecular Formula	m.p. (°C)	$[\alpha]_D^{20}$
1	Ph	H	2	1	CH <sub>2</sub>		C <sub>21</sub> H <sub>23</sub> N·HCl	>240	-
2	Ph	H	2	1	CH <sub>2</sub>		C <sub>22</sub> H <sub>27</sub> NO	107-108	-
3	Ph	H	2	1	CH <sub>2</sub>		C <sub>22</sub> H <sub>27</sub> N·HCl	264-265	-

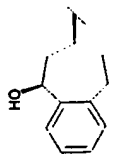
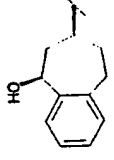
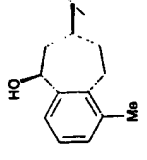
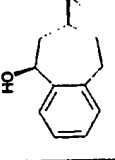
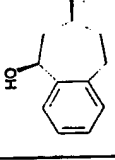
4	Ph	H	2	1	CH <sub>2</sub>		C <sub>22</sub> H <sub>25</sub> NO·HCl	261-262	-
5	Ph	H	2	1	CH <sub>2</sub>		C <sub>22</sub> H <sub>25</sub> NO·HCl	259-260	-11.30 (c=0.1, MeOH)
6	Ph	H	2	1	CH <sub>2</sub>		C <sub>22</sub> H <sub>25</sub> NO·HCl	257-258	+11.74 (c=0.1, MeOH)
7	Ph	H	2	1	CH <sub>2</sub>		C <sub>26</sub> H <sub>27</sub> NO·HCl	-	-
8	Ph	H	2	1	CH <sub>2</sub>		C <sub>22</sub> H <sub>25</sub> N·HCl	239-240	-
9	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>29</sub> NO	48-50	-

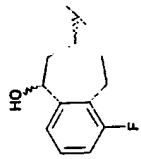
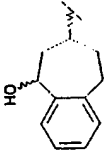
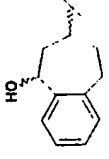
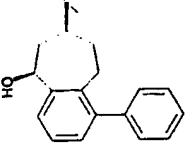
10	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO <sub>2</sub>	46-48	-
11	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO <sub>2</sub>	45-48	-
12	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>27</sub> NO·HCl	220 (dec)	-
13	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>29</sub> NO <sub>2</sub> ·HCl	140-143	-
14	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>29</sub> NO <sub>2</sub> ·HCl	185-188	-

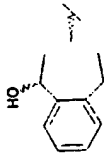
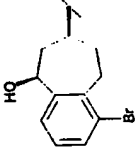
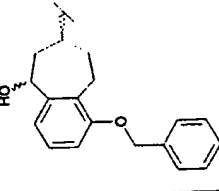
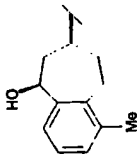
15	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO·HCl	213-215	-
16	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO·HCl	220-222	-
17	Ph	H	2	1	Bond		C <sub>20</sub> H <sub>23</sub> N·HCl	>250	-
18	Ph	H	2	1	Bond		C <sub>22</sub> H <sub>27</sub> N·HCl	>250	-
19	(2-Me)Ph	H	2	1	CH <sub>2</sub>		C <sub>25</sub> H <sub>33</sub> NO·HCl	>250	-

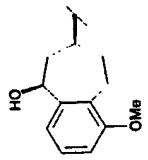
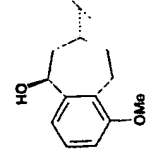
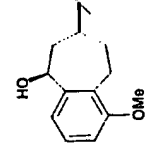
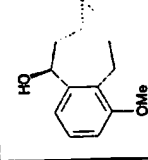


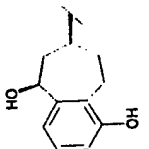
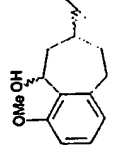
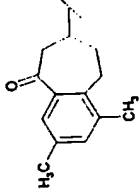
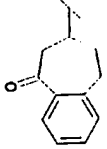
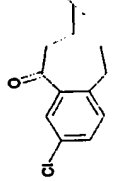
20	Ph	H	2	1	CH <sub>2</sub>		C <sub>25</sub> H <sub>33</sub> NO	52-55	-
21	(2-OMe)Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO <sub>2</sub>	72-74	-
22	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>28</sub> ClNO	-	-
23	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>28</sub> ClNO	-	-
24	(2-OH)Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>29</sub> NO <sub>2</sub> .HCl	158-160	-

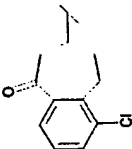
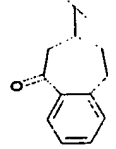
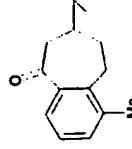
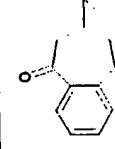
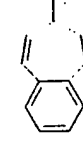
25	(3-F)Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>28</sub> FNO.HCl	238-240	-
26	(2-Me)Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO.HCl	>250	-
27	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO	52-55	-
28	(4-OBn)Ph	H	2	1	CH <sub>2</sub>		C <sub>30</sub> H <sub>35</sub> NO <sub>2</sub> .HCl	225-228	-
29	(3-Br)Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>28</sub> BrNO.HCl	>250	-



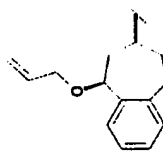
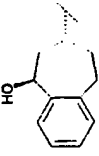
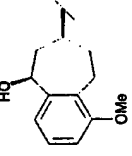
30	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>28</sub> FNO.HCl	218-220	-
31	(4-F)Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>28</sub> FNO.HCl	227-229	-
32	(3,5-di- OMe)Ph	H	2	1	CH <sub>2</sub>		C <sub>25</sub> H <sub>33</sub> NO <sub>3</sub> .HCl	223-225	-
33	Ph	H	2	1	CH <sub>2</sub>		C <sub>29</sub> H <sub>33</sub> NO.HCl	245-246	-

34	(2-Cl)Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>28</sub> ClNO.HCl	239-240	-
35	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>28</sub> BrNO.HCl	220-224	-
36	Ph	H	2	1	CH <sub>2</sub>		C <sub>30</sub> H <sub>35</sub> NO <sub>2</sub> .HCl	198-202	-
37	(3-F)Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>30</sub> FNO.HCl	241-243	-

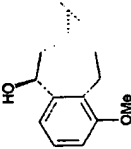
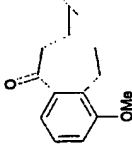
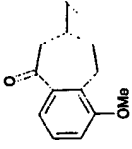
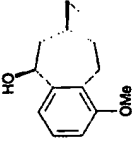
38	(2-Me)Ph	H	2	1	CH <sub>2</sub>		C <sub>25</sub> H <sub>33</sub> NO <sub>2</sub>	-	-	-
39	(2-Me)Ph	H	2	1	CH <sub>2</sub>		C <sub>25</sub> H <sub>33</sub> NO <sub>2</sub>	-	-	-
40	(3-F)Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>30</sub> FNO <sub>2</sub>	-	-	-
41	(3-F)Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>30</sub> FNO <sub>2</sub>	-	-	-

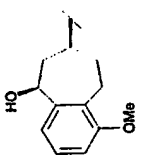
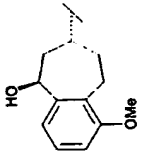
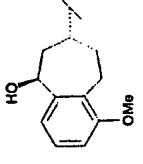
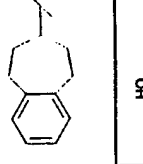
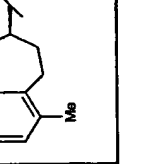
42	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>29</sub> NO <sub>2</sub> .HCl	190-193	-
43	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO <sub>2</sub>	176-189	-
44	Ph	H	2	1	CH <sub>2</sub>		C <sub>25</sub> H <sub>31</sub> NO.HCl	222-225	-
45	(2-OMe)Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>29</sub> NO <sub>2</sub> .HCl	232-234	-
46	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>26</sub> ClNO.HCl	180-185	-


47	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>26</sub> ClNO.HCl	-	-
48	(2-OH)Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>27</sub> NO <sub>2</sub> .HCl	216-218	-
49	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>29</sub> NO.HCl	205-210	-
50	(2-Me)Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>29</sub> NO	202-205	-
51	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>27</sub> N.HCl	>250	-

52	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>29</sub> N.HCl	>250	-
53	(2-Me)Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> N	245	-
54	Ph	H	2	1	CH <sub>2</sub>		C <sub>26</sub> H <sub>33</sub> NO.HCl	126-128	-
55	Ph	H	2	1	CH <sub>2</sub>		C <sub>23</sub> H <sub>29</sub> NO.HCl	>250	-
56	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO <sub>2</sub> .HCl	229-231	-



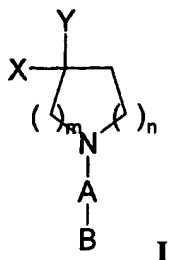
57	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO <sub>2</sub> .HCl	>250	-
58	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>29</sub> NO <sub>2</sub> .HCl	-	+27.14 (c=0.1, MeOH)
59	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>29</sub> NO <sub>2</sub> .HCl	-	-29.14 (c=0.1, MeOH)
60	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO <sub>2</sub> .HCl	-	+64.2 (c=0.1, EtOH/Hexane)

61	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO <sub>2</sub> .HCl	-	-65.8 (c=0.1, EtOH/Hexane)
62	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO <sub>2</sub>	-	+12.7 (c=0.5, EtOH)
63	Ph	H	2	1	CH <sub>2</sub>		C <sub>24</sub> H <sub>31</sub> NO <sub>2</sub>	-	-12.1 (c=0.5, EtOH)
64	(2-Me)Ph	H	2	1	Bond		C <sub>23</sub> H <sub>29</sub> N	-	-
65	(2-Me)Ph	H	2	1	CH <sub>2</sub>		C <sub>25</sub> H <sub>33</sub> NO	-	-49 (c= 0.1, EtOH/Hexane)

66	(2-Me)Ph	H	2	1	CH <sub>2</sub>		C <sub>25</sub> H <sub>33</sub> NO	-	+40 (c= 0.1, EtOH/Hexane)
----	----------	---	---	---	-----------------	--	------------------------------------	---	------------------------------

# Claims

1. A compound of formula I, or a salt thereof or a hydrate thereof



5

wherein

- X and Y are selected independently from hydrogen and aryl, which aryl is unsubstituted or substituted one or more times by hydroxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, aryl, heterocyclyl, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or halo, which alkyl or alkoxy groups are unsubstituted or substituted one or more times by halo;
- m and n are independently 0 to 3, provided that m and n are not both 0;
- A represents a single bond or is -(CR<sub>pa</sub>R<sub>pb</sub>)<sub>p</sub>- wherein p is 1-3 and R<sub>pa</sub> and R<sub>pb</sub> are selected independently from hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy and halo, which alkyl or alkoxy groups are independently substituted one or more times by halo;
- B represents a C<sub>4-8</sub> saturated or unsaturated ring, which ring is unsubstituted or substituted one or more times by C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkenoxy, aryl, aryloxy, hydroxy, oxo, halo, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, and C<sub>1-6</sub>alkylamido, which C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy groups are unsubstituted or substituted one or more times by halo, which aryl group is unsubstituted or substituted one or more times by aryl, heterocyclyl, aryloxy, arylC<sub>1-6</sub>alkoxy, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkenoxy, C<sub>1-6</sub>alkoxy, halo, or C<sub>1-6</sub>alkyl, which C<sub>1-6</sub>alkyl may be substituted one or more times by halo, and which aryl group is linked to said ring by a single bond or is benzo-condensed therewith; subject to the proviso that the compounds on List A are excluded.

2. An enantiomer of a compound of formula I according to claim 1.
3. A mixture of enantiomers of a compound of formula I according to claim 1 wherein one enantiomer is present in a greater proportion than its antipode.
4. A compound according to claim 1 selected from:

- (±)-7-[(4-Phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- (±)-7-*cis*-[(4-Phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- 5 (±)-2-[(4-Phenylpiperidin-1-yl)methyl]-1,2-dihydronaphthalene;
- (±)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene;
- (R)-(-)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene;
- (±)-2-[(4-Phenylpiperidin-1-yl)methyl]-1,2,3,4-tetrahydro naphthalene;
- (S)-(+)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-oxo-2H-3,4-dihydronaphthalene;
- 10 (±)-3-[(4-Phenylpiperidin-1-yl)methyl]-1-hydroxy-2H-3,4-dihydronaphthalene;
- (±)-1,2-Dihydro-2-[(4-phenylpiperidin-1-yl)methyl]phenanthren-4-(3H)-one;
- 1-(2,3-Dihydro-1H-inden-2-yl)-4-phenylpiperidine;
- (±)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- 15 (±)-3-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- (±)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- (±)-3-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- 20 (±)-*cis*-5-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene;
- (±)-*trans*-5-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene;
- 25 2,3-Dihydro-2-[(4-phenylpiperidin-1-yl)methyl]indene;
- N-(6,7,8,9-Tetrahydro-5H-benzocyclohepten-7-yl)-4-phenylpiperidine;
- (±)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- (±)-1,3-Dimethyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- 30 (±)-*cis*-7-[[4-(2-Methoxyphenyl)piperidin-1-yl]methyl]-6,7,8,9- tetrahydro-5H-benzocyclohepten-5-ol;
- (±)-*cis*-3-Chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- 35 (±)-1-Chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- (±)-7-[[4-(2-Hydroxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;

- (±)-*cis*-7-[[4-(3-Fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*cis*-7-[[4-(2-Methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
5 (±)-*cis*-1-Methyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*cis*-7-[[4-(4-Benzyloxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*cis*-7-[[4-(3-Bromophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
10 (±)-1-Fluoro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-7-[[4-(4-Fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-7-[[4-(3,5-Dimethoxyphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
15 (±)-*cis*-1-Phenyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-7-[[4-(2-Chlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
20 (±)-*cis*-1-Bromo-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-1-Benzyloxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
25 (±)-*cis*-1-Methyl-7-[[4-(3-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*cis*-1-Methoxy-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*trans*-1-Methoxy-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
30 (±)-*cis*-1-Methoxy-7-[[4-(3-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-*trans*-1-Methoxy-7-[[4-(3-fluorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
35 (±)-*cis*-1-Hydroxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;  
(±)-4-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;

- (±)-1,3-Dimethyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- (±)-7-[[4-(2-Methoxyphenyl)piperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- 5 (±)-3-Chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- (±)-1-Chloro-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- (±)-7-[[4-(2-Hydroxyphenyl)piperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- 10 (±)-1-Methyl-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- (±)-7-[[4-(2-Methylphenyl)piperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- 15 (±)-7-[(4-Phenylpiperidin-1-yl)methyl]-6,7-dihydro-5H-benzocycloheptene;
- 7-[(4-Phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene;
- 7-[[4-(2-Methylphenyl)piperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene;
- (±)-*cis*-5-Allyloxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocycloheptene;
- 20 (±)-*trans*-7-[(4-Phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- (±)-*cis*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- 25 (±)-*trans*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- (+)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- (-)-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one;
- 30 (+)-*cis*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- (-)-*cis*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- 35 (+)-*trans*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- (-)-*trans*-1-Methoxy-7-[(4-phenylpiperidin-1-yl)methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol;
- [4-(2-Methylphenyl)-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-7-

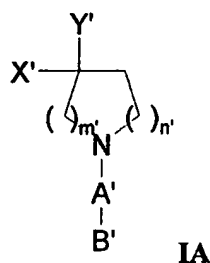
yl)]piperidine;

(-)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol, and;

- 5 (+)-*cis*-1-Methyl-7-[[4-(2-methylphenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol.

5. A compound of formula I as defined in claim 1, for use as an active therapeutic substance.

- 10 6. A method of modulating the ORL-1 receptor activity in a human or animal patient in need thereof, which method comprises administering to the human or animal patient an effective amount of a compound of formula IA



15

wherein

X', Y', A', B', m', and n' are as defined for X, Y, A, B, m, and n respectively in formula I of claim 1;

including the compounds of List A.

20

7. Use of a compound of formula IA as defined in claim 6 in the manufacture of a medicament for administration to a human or animal patient for modulating the ORL-1 receptor activity.

25

8. Use of an antagonist of formula I as defined in claim 1 as an analgesic in humans or animals for the treatment, for example, of acute pain; chronic neuropathic or inflammatory pain, including post herpetic neuralgia, neuralgia, diabetic neuropathy and post stroke pain; osteoarthritis/back pain; and painful pregnancy labour.

30

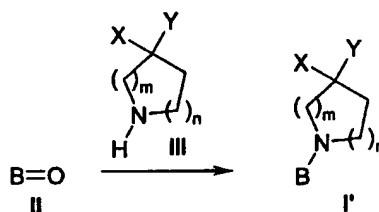
9. Use of a compound of formula I as defined in claim 1 in the treatment or prophylaxis of eating disorders, such as anorexia and bulimia; anxiety and stress conditions; immune system diseases; cardiovascular system dysfunctions; memory



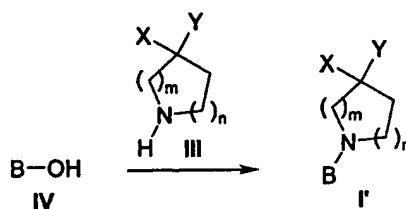
loss, cognitive disorders, motor impairment and neurodegeneration owing to Alzheimer's disease, senile dementia, Parkinson's disease or other neurodegenerative pathologies; stroke; epilepsy; altered diuresis and sodium excretion; syndrome of inappropriate secretion of antidiuretic hormone (SIADH);  
 5 adult respiratory distress syndrome (ARDS); congestive heart failure; cirrosis with ascites; sexual dysfunctions including impotence and frigidity; and altered pulmonary function, including chronic obstructive pulmonary disease.

10. A pharmaceutical composition comprising a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable hydrate thereof, and a pharmaceutically acceptable carrier.

11. A process for the preparation of a compound of formula I, where A in formula I as defined in claim 1 is a bond (formula I'), which process comprises:  
 15 a). reacting a ketone of formula II with an amine of formula III under reductive amination conditions



20 wherein B, m, n, X and Y are defined in accordance with formula I in claim 1, or  
 b). transforming an alcohol of formula IV into a suitable leaving group and subsequent reaction with an amine of formula III,



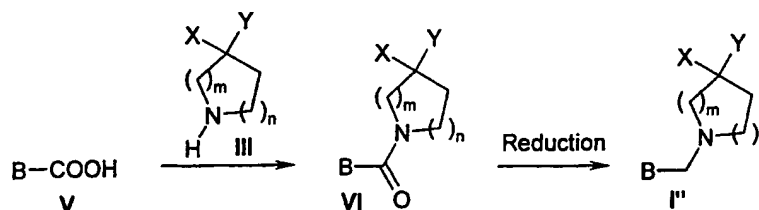
25 wherein B, m, n, X and Y are defined in accordance with formula I in claim 1.

12. A process for the preparation of a compound of formula I, where A in formula I as defined in claim 1 is a group  $-(CR_{pa}R_{pb})_p-$  and p is 1 and  $R_{pa}$  and  $R_{pb}$

30

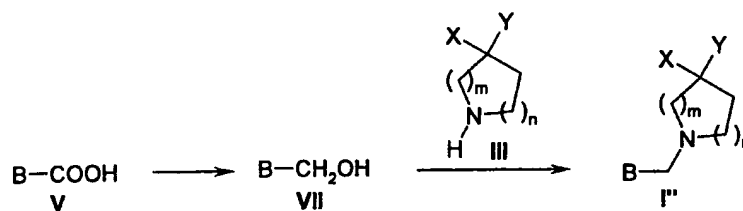
are both hydrogen (formula I''), which process comprises

a) reacting a carboxylic acid of formula V with an amine of formula III, and thereafter reducing the resulting amide of formula VI,



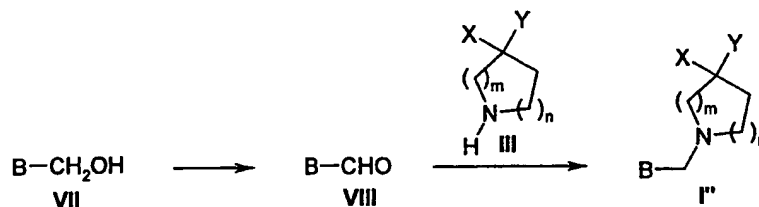
wherein B, m, n, X and Y are defined in accordance with formula I in claim 1, or

b) reducing a carboxylic acid of formula V to an alcohol of formula VII, and reacting said alcohol with an amine of formula III,



wherein B, m, n, X and Y are defined in accordance with formula I in claim 1, or

c) oxidizing an alcohol of formula VII to an aldehyde of formula VIII, and reacting said aldehyde with an amine of formula III under reductive amination conditions,

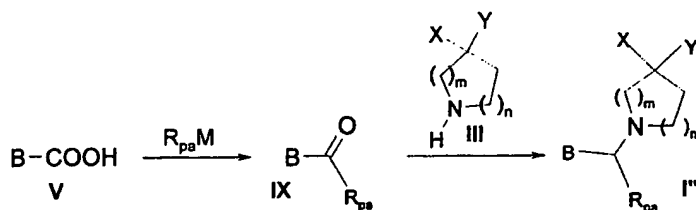


wherein B, m, n, X and Y are defined in accordance with formula I in claim 1.

20 13. A process for the preparation of a compound of formula I, where A in formula I as defined in claim 1 is a group  $-(CR_{pa} R_{pb})_p-$  and p is 1,  $R_{pa}$  is a  $C_{1-6}$  alkyl group and  $R_{pb}$  is hydrogen (formula I'''), which process comprises

a) reacting a carboxylic acid or a derivative thereof of formula V with an  
25 organometallic compound of formula  $R_{pa}M$ , and thereafter reacting the resulting

carbonylic compound **IX** with an amine of formula **III** under reductive amination conditions,



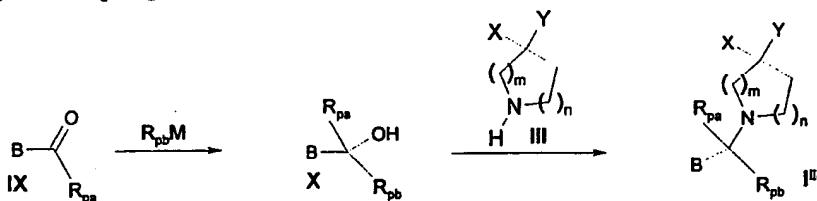
5

wherein B, R<sub>1p</sub>, m, n, X and Y are defined in accordance with formula **I** in claim 1.

14. A process for the preparation of a compound of formula **I**, where A in formula **I** as defined in claim 1 is a group -(CR<sub>pa</sub>R<sub>pb</sub>)<sub>p</sub>- and p is 1, and R<sub>pa</sub> and R<sub>pb</sub> are both C<sub>1-6</sub> alkyl groups (formula **I'''**), which process comprises

10

a) reacting a carbonylic compound of formula **IX** with an organometallic of formula R<sub>pb</sub>M, and coupling the resulting alcohol of formula **X** with an amine of formula **III**

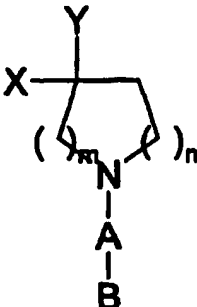


15

wherein B, R<sub>pa</sub>, R<sub>pb</sub>, m, n, X and Y are defined in accordance with formula **I** in claim 1.



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C07D 211/14, 211/22, 211/18,</b> <b>A61K 31/445, A61P 25/00, 25/04</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 00/27815</b>  <b>(43) International Publication Date:</b> 18 May 2000 (18.05.00)
<b>(21) International Application Number:</b> PCT/EP99/08706  <b>(22) International Filing Date:</b> 10 November 1999 (10.11.99)  <b>(30) Priority Data:</b> MI98A002442 11 November 1998 (11.11.98) IT  <b>(71) Applicant (for all designated States except US):</b> SMITHKLINE BEECHAM SPA [IT/IT]; Via Zambelletti, I-20021 Baranzate di Bollate (IT).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BARLOCCO, Daniela [IT/IT]; Università degli Studi di Milano, Istituto di Chimica Farmaceutica E Tossicologica, Viale Abruzzi, 42, I-20131 Milan (IT). CIGNARELLA, Giorgio [IT/IT]; Università degli Studi di Milano, Istituto di Chimica Farmaceutica E Tossicologica, Viale Abruzzi, 42, I-20131 Milan (IT). GIARDINA, Guiseppe, Arnaldo, Maria [IT/IT]; SmithKline Beecham Spa, Via Zambelletti, I-20021 Baranzate di Bollate (IT). GRUGNI, Mario [IT/IT]; SmithKline Beecham Spa, Via Zambelletti, I-20021 Baranzate di Bollate (IT). RONZONI, Silvano [IT/IT]; SmithKline Beecham Spa, Via Zambelletti, I-20021 Baranzate di Bollate (IT).		<b>(74) Agent:</b> RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).  <b>(81) Designated States:</b> CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>  <b>(88) Date of publication of the international search report:</b> 26 October 2000 (26.10.00)
<b>(54) Title:</b> N-SUBSTITUTED AZACYCLES, THEIR PREPARATION AND THEIR USE AS ORL-1 RECEPTOR LIGANDS  <div style="text-align: center;">  <div style="position: absolute; left: 610px; top: 600px;">(I)</div> </div>		
<b>(57) Abstract</b>  <p>Compounds of formula (I) or a salt thereof or a hydrate thereof, as follows: wherein X and Y are selected independently from hydrogen and aryl, which aryl is unsubstituted or substituted one or more times by hydroxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, aryl, heterocyclyl, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or halo, which alkyl or alkoxy groups are unsubstituted or substituted one or more times by halo; m and n are independently 0 to 3, provided that m and n are not both 0; A represents a single bond or is -(CR<sub>pa</sub> R<sub>pb</sub>)<sub>p</sub> wherein p is 1-3 and R<sub>pa</sub> and R<sub>pb</sub> are selected independently from hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy and halo, which alkyl or alkoxy groups are independently substituted one or more times by halo; B represents a C<sub>4-8</sub> saturated or unsaturated ring, which ring is unsubstituted or substituted one or more times by C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, aryl, aryloxy, hydroxy, oxo, halo, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, and C<sub>1-6</sub>alkylamido, which C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy groups are unsubstituted or substituted one or more times by halo, which aryl group is unsubstituted or substituted one or more times by aryl, heterocyclyl, aryloxy, arylC<sub>1-6</sub>alkoxy, amino, C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, arylC<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkenoxy, C<sub>1-6</sub>alkoxy, halo, or C<sub>1-6</sub>, which C<sub>1-6</sub>alkyl may be substituted one or more times by halo, and which aryl group is linked to said ring by a single bond or is benzo-condensed therewith are ligands of the ORL-1 receptor.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/08706

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/14 C07D211/22 C07D211/18 A61K31/445 A61P25/00  
A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, EPO-Internal, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 812 119 A (WALKER G.N.) 21 May 1974 (1974-05-21) cited in the application claims 1,2; examples 16,19,21 ---	1,5,10
X	US 4 022 791 A (WELCH JR., W.M.) 10 May 1977 (1977-05-10) cited in the application column 13 -column 14; claims 1,6,7,9; examples 4-7 --- -/--	1,5,8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 July 2000

Date of mailing of the international search report

25.07.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3018

Authorized officer

Hartrampf, G

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/08706

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WELCH W.M. ET AL.: "Analgesic and tranquilizing activity of 5,8-disubstituted 1-tetralone mannich bases" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, vol. 20, no. 5, May 1977 (1977-05), pages 257-263, XP000882092 cited in the application compounds II,III and 1,2,5,6,22-31,42,43, 46-48	1,5,8
X	--- DE 28 34 372 A (E.R. SQUIBB & SONS, INC.) 15 February 1979 (1979-02-15) compounds of formulae (V) and (XVIII) claim 25; examples 5,26,27,30,89,91	1
X	--- GB 2 091 250 A (DELALANDE SA) 28 July 1982 (1982-07-28) code number 96 and 97 claims 1,3,4,7,8	1,5,8
X	--- DE 36 20 358 A (IMPERIAL CHEMICAL INDUSTRIES PLC) 18 December 1986 (1986-12-18) compounds no. 1,3-6,8,10,15,19,21,23,25, 27,29,31,37,39,41,43,46,47 table I	1
X	--- GB 2 177 085 A (IMPERIAL CHEMICAL INDUSTRIES PLC) 14 January 1987 (1987-01-14) cited in the application compound no. 5,20-25,31-35,41-45,51-55, 61-65,71-75,81-85,91,93,95,97,99-106,115, 116,119,120,126,128	1
X	--- SANTANA L. ET AL.: "Sintesis de 2-aminometiltetralinas como agentes .alpha.-bloquantes y antidopaminérgicos" ANALES DE LA REAL ACADEMIA DE FARMACIA, vol. 55, April 1989 (1989-04), pages 461-469, XP000882145 cited in the application compounds IIb and IVb page 463; table 1	1,5
X	--- EP 0 825 180 A (DAINIPPON PHARMACEUTICAL CO., LTD.) 25 February 1998 (1998-02-25) compounds of formulae (I), (II) and (VI) claims 1-15; examples 1-48,52,54,55,58,59,62,64,65,68,70	1,5,10
	--- -/--	

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/EP 99/08706

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 02432 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 22 January 1998 (1998-01-22) cited in the application claims 8,11-17,20,24-29 ---	1,5,10
X	WO 98 36749 A (BRISTOL-MYERS SQUIBB COMPANY) 27 August 1998 (1998-08-27) cited in the application examples 3,4,7,14-16,22,23,55-59,61,63,64,74-77,79, 80,84-91,93,94,96-112,114,115,122,138,202 claims 1-4 ---	1,2,5,10
E	WO 00 06545 A (SCHERING CORPORATION) 10 February 2000 (2000-02-10) claims 1-3,10,11 ---	1,5-7,10
A	MEUNIER J.-C.: "Nociceptin/orphanin FQ and the opioid receptor-like ORL1 receptor" EUROPEAN JOURNAL OF PHARMACOLOGY, NL, ELSEVIER SCIENCE B.V. AMSTERDAM, vol. 340, January 1997 (1997-01), pages 1-15, XP000872550 ISSN: 0014-2999 the whole document ---	1-7,10
A	HENDERSON G. & MC KNIGHT T.: "The orphan opioid receptor and its endogenous ligand - nociceptin/orphanin FQ" TRENDS IN PHARMACOLOGICAL SCIENCES, GB, ELSEVIER SCIENCE LTD., CAMBRIDGE, vol. 18, no. 8, 1 August 1997 (1997-08-01), pages 293-300, XP004085920 ISSN: 0165-6147 the whole document ---	1-7,10
A	ZAKI P.A. & EVANS C.J.: "ORL-1: An awkward child of the opioid receptor family" THE NEUROSCIENTIST, US, BALTIMORE, MD, vol. 4, no. 3, March 1998 (1998-03), pages 172-184, XP000872580 ISSN: 1073-8584 the whole document -----	1-7,10



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 99/08706

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-3  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:  
  
1-8, 10-14
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Claims Nos.: 1-3

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to compounds mentioned in claim 4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7,10-14

Compounds of formula (I), their preparation, and the pharmaceutical composition and use as modulators of ORL-1 receptor activity of compounds of formula (IA) including those of formula (I)

2. Claim : 8

The use of compounds of formula (I) as analgesics independently defined from ORL-1 receptor modulation

3. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or prophylaxis of eating disorders independently defined from ORL-1 receptor modulation

4. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or prophylaxis of anxiety and stress conditions independently defined from ORL-1 receptor modulation

5. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or prophylaxis of immune system diseases independently defined from ORL-1 receptor modulation

6. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or prophylaxis of cardiovascular system dysfunctions independently defined from ORL-1 receptor modulation

7. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or prophylaxis of neurodegenerative pathologies independently defined from ORL-1 receptor modulation

8. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

prophylaxis of stroke independently defined from ORL-1  
receptor modulation

9. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or  
prophylaxis of epilepsy independently defined from ORL-1  
receptor modulation

10. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or  
prophylaxis of altered diuresis and sodium excretion  
independently defined from ORL-1 receptor modulation

11. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or  
prophylaxis of SIADH independently defined from ORL-1  
receptor modulation

12. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or  
prophylaxis of ARDS independently defined from ORL-1  
receptor modulation

13. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or  
prophylaxis of congestive heart failure independently  
defined from ORL-1 receptor modulation

14. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or  
prophylaxis of cirrosis with ascites independently defined  
from ORL-1 receptor modulation

15. Claim : 9(part)

Use of the compounds of formula (I) in the treatment or  
prophylaxis of sexual dysfunction independently defined from  
ORL-1 receptor modulation

16. Claim : 9(part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of the compounds of formula (I) in the treatment or prophylaxis of altered pulmonary function independently defined from ORL-1 receptor modulation

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/08706

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3812119	A	21-05-1974	NONE	
US 4022791	A	10-05-1977	NONE	
DE 2834372	A	15-02-1979	US 4156723 A	29-05-1979
			US 4173640 A	06-11-1979
			FR 2399406 A	02-03-1979
			GB 2005247 A,B	19-04-1979
			GB 2037287 A,B	09-07-1980
			GB 2037288 A,B	09-07-1980
			JP 54036240 A	16-03-1979
GB 2091250	A	28-07-1982	FR 2496653 A	25-06-1982
			FR 2518087 A	17-06-1983
			AU 7875781 A	01-07-1982
			BE 891526 A	18-06-1982
			CA 1181748 A	29-01-1985
			DE 3150876 A	29-07-1982
			ES 508670 D	01-06-1983
			ES 8306093 A	01-08-1983
			ES 518692 D	01-11-1983
			ES 8400093 A	01-01-1984
			ES 518693 D	01-11-1983
			ES 8400388 A	16-01-1984
			GB 2137992 A,B	17-10-1984
			GR 78081 A	26-09-1984
			IT 1168074 B	20-05-1987
			JP 57128660 A	10-08-1982
			LU 83850 A	02-09-1983
			NL 8105791 A	16-07-1982
			SE 8107537 A	23-06-1982
			US 4386090 A	31-05-1983
			US 4431851 A	14-02-1984
			US 4504663 A	12-03-1985
			ZA 8108847 A	24-11-1982
DE 3620358	A	18-12-1986	AU 5785986 A	24-12-1986
			DK 285286 A	19-12-1986
			FR 2583264 A	19-12-1986
			GB 2176780 A	07-01-1987
			JP 61291576 A	22-12-1986
			US 4777176 A	11-10-1988
			ZA 8603843 A	25-02-1987
GB 2177085	A	14-01-1987	AU 5835586 A	24-12-1986
			DE 3620356 A	18-12-1986
			DK 285786 A	19-12-1986
			FR 2583263 A	19-12-1986
			JP 61293953 A	24-12-1986
			US 4785006 A	15-11-1988
			ZA 8604131 A	25-02-1987
EP 0825180	A	25-02-1998	AU 704728 B	29-04-1999
			AU 5288496 A	07-11-1996
			BR 9608332 A	23-02-1999
			NO 974745 A	12-12-1997
			PL 322783 A	16-02-1998
			RU 2142453 C	10-12-1999

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/EP 99/08706

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0825180 A		SK 137597 A	06-05-1998
		US 5847159 A	08-12-1998
		CA 2218330 A	24-10-1996
		CZ 9703249 A	18-02-1998
		HU 9800633 A	28-06-1999
		WO 9633169 A	24-10-1996
-----			
WO 9802432 A	22-01-1998	AU 3460797 A	09-02-1998
		JP 10338672 A	22-12-1998
-----			
WO 9836749 A	27-08-1998	AU 6148698 A	09-09-1998
		US 6048877 A	11-04-2000
-----			
WO 0006545 A	10-02-2000	AU 5205699 A	21-02-2000
-----			